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The Effects of Historical Alcohol Use on Neuropsychological Functioning in Older Adults Following a Traumatic Brain Injury

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The Effects of Historical Alcohol Use on Neuropsychological Functioning in Older Adults Following a Traumatic Brain Injury

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*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

The Doctorate Program in Clinical Psychology
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CERTIFICATE OF APPROVAL

Clinical Research Project

This is to certify that the Clinical Research Project of

Ryan W. Sever

has been approved by the
CRP Committee on May 13, 2019
as satisfactory for the CRP requirement
for the Doctor of Psychology degree
with a major in Clinical Psychology

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Abstract

The present study aimed to determine the effects of alcohol abuse and dependence in long term functioning of older adults who have experienced a moderate to severe traumatic brain injury. The research question being answered in the current study was if a history of alcohol abuse or dependence would worsen neuropsychological functioning in older adults who experienced at least one moderate to severe traumatic brain injury. Participants of the study were selected from the more extensive database provided by the Brain Aging in Vietnam War Veterans (DOD-ADNI) database. All participants were Vietnam War veterans between the ages of 61 and 85. The participants were grouped according to presence of a traumatic brain injury and history of alcohol use or dependence. All participants had at least five years of abstinence from alcohol. Neuropsychological tests measured differences between groups in the domains of verbal fluency, confrontation naming, verbal memory, executive functioning, and mood. Results of the current study showed there was no difference in neuropsychological functioning between individuals with a history of traumatic brain injury and individuals with a history of traumatic brain injury and alcohol abuse or dependence. The results of the current study indicate that in a population of older adults with a history of traumatic brain injury, neuropsychological functioning deficits are no greater if the individual also has a history of alcohol use.

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CHAPTER I: INTRODUCTION

It is estimated that every year approximately 1.7 million individuals in the United States experience a traumatic brain injury (TBI; Faul, Xu, Waldo, & Coronado, 2010). Between the years 2007 and 2013, there were around 2.8 million emergency department visits as a result of TBI in the United States (Taylor, Bell, Breiding, & Xu, 2017). Approximately 6% of Americans who sustain a TBI experience permanent disability as a result (Langlois, Rutland-Brown, & Thomas, 2004). The direct and indirect societal cost of TBI is likely to be over $60 billion per year (Finkelstein, Corso, & Miller, 2006; Zitney et al., 2008). The presence of TBI history can have negative consequences throughout the life of an injured individual. For instance, executive dysfunction following TBI may limit the ability to accomplish instrumental activities of daily living (Colantonio et al., 2004; Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009) and lead to employment difficulties (Ownsworth & McKenna, 2004; Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009).

Traumatic brain injury is often referred to as the signature wound of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF; Jones, Fear, and Wessely, 2007; Snell & Halter, 2010; Wieland, Hursey, & Delgado, 2010). The Department of Defense (2017) estimates that approximately 361,000 service members experienced at least one TBI during the years of 2000 through 2016. The astounding number of traumatic brain injuries has increased from 12% of all Vietnam War causalities to 22% of all OIF/OEF casualties being due to head trauma (U.S. Department of Veterans Affairs, 2018).

General intelligence, as well as verbal and nonverbal IQ, is lower in individuals following a TBI (Kinnunen et al., 2011). Diminished executive functioning is a commonly cited change following TBI. Areas of functioning commonly impacted include planning (Shum et al.,

2009; Levin & Kraus, 1994; Miller, 2000), judgment, and cognitive aspects of decision making (Rabinowitz & Levin, 2014). Sustained attention (Chan, 2005; Vanderploeg, Curtiss, & Belanger, 2005; Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009; Ponsford & Kinsella, 1992) and divided attention (Mangels, Craik, Levine, Schwartz, & Stuss, 2002) have also been found to be impaired following a TBI. Processing speed is slower following a TBI (Kinnunen et al., 2011). Memory acquisition and retrieval are also negatively impacted following a TBI (Dikmen et al., 2009; Stuss & Alexander, 2000). Behavioral components such as low motivation (Rabinowitz & Levin, 2014) and poor emotional regulation (Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009) are also found in individuals following a TBI.

Computed tomography (CT) is the imaging modality of choice for during the acute phase of injury, but may not be sensitive to more mild forms of TBI during the first 24 hours (Bigler & Maxwell, 2012). CT scans of an injured brain may reveal abnormalities such as petechial hemorrhages, subarachnoid hemorrhages, or evidence of contusion (American Psychiatric Association, 2013). Magnetic resonance imaging (MRI) can detect nonhemorrhagic damage, such as cortical contusions and traumatic axonal injuries (Kim & Gean, 2011). The use of gradient-echo imaging allows for the identification of hyperintensities suggestive of microbleeds (Kinnunen et al., 2011) which are an indication of diffuse axonal injury (Schneid, Preul, Gruber, Wiggins, & Von Cramon, 2003). The utility of MRI comes in the subacute and chronic phases of TBI in which differing contrasts can provide input into secondary damage (Gallagher, Hutchinson, & Pickard, 2007; Aquino, Woolen, & Steenberg, 2015). Diffuse Tensor Imaging (DTI) shows that lower fractional anisotropy was associated with the loss of myelinated axons (Laitinen, Sierra, Bolkvadze, Pitkanen, & Grohn, 2015).

According to the 2015 National Survey on Drug Use and Health (Center for Behavioral Health Statistics and Quality, 2016), 15.1 million adults meet criteria for alcohol use disorder. 70.1% of the population sampled in the aforementioned study endorsed consuming alcohol at some point during the previous year with 26.9% reporting drinking five or more (males) or four or more (females) alcoholic beverages during one occasion during the previous month.

Heavy drinking is endorsed by one in six service members (Bray & Hourani, 2007) and approximately 15% of soldiers returning from combat deployments in Iraq (Operation Iraqi Freedom; OIF) and Afghanistan (Operation Enduring Freedom [OEF]) report alcohol-related problems after deployment (Jacobson et al., 2008). Military personnel who deploy to areas of conflict are at an increased risk for alcohol use disorder compared to personnel who do not deploy (Kelsall et al., 2015). According to the National Institute on Drug Abuse (NIDA; 2013), there has been a 13% increase in binge drinking amongst active duty service members from 1998 to 2008. In 2008, 20% of active duty military endorsed weekly binge drinking (NIDA, 2013). High amounts of combat experience appear to increase the likelihood of binge drinking (NIDA, 2013). In one particular study, 3.1% of military personnel met criteria for alcohol use disorder and an additional 36.9% participated in binge drinking (Trautmann, Schonfeld, Behrendt, Hofler, Zimmermann, & Wittchen, 2013). The 36.9% of military personnel is substantially larger than the 26.9% of civilians who participate in binge drinking (Center for Behavioral Health Statistics and Quality, 2016). Men in the military were 3.5 times more likely to report frequent heavy alcohol consumption compared to female counterparts (Bray & Hourani, 2007). Army, Navy, and Marine Corps personnel were more likely than Air Force personnel to report frequent heavy drinking (Bray & Hourani, 2007). Heavy alcohol consumption among military personnel increased by 5%, and binge drinking increased by 12% between 1998 and 2008 (Bray, Brown,

&Williams, 2013). One study found that 35% of Vietnam veterans met criteria for alcohol dependence at some point during the 25 years following the Vietnam War (Jacob, Blonigen, Koenig, Wachsmuth, & Price, 2010). The prevalence for Vietnam veterans is slightly higher than the 29.1% of individuals who have met criteria for an alcohol use disorder at some point during their life (Grant et al., 2015).

In terms of overall functioning, nonverbal tasks appear to be compromised more significantly than verbal tasks (Parsons & Leber, 1981). Executive functioning deficits have been found in chronic alcohol users (Scheurich, 2005) but returned to normal levels of functioning following six months of abstinence (Pitel et al., 2009). Attention and working memory deficits are also commonly seen in chronic alcohol users (Scheurich, 2005); however, improved attention has been observed following 5-6 weeks of abstinence (Bendszus et al., 2001). Processing speed is also slower in individuals who meet criteria for alcohol use disorder (Sher, Martin, Wood, & Rutledge, 1997). Both verbal and nonverbal recall is impacted by alcohol abuse (Brown, Tapert, Grahholm, & Delis, 2000). Deficits in visuospatial abilities are commonly seen following alcohol abuse (Bowden & McCarter, 1993; Ellis & Oscar-Burman, 1989; Parsons, 1987; Scheurich, 2005). Perceptual-motor deficits have also been noted following prolonged alcohol abuse (Bowden & McCarter, 1993; Ellis & Oscar-Burman, 1989; Parsons, 1987). Undifferentiated affective response to emotional stimuli is typical in chronic alcohol abusers, which lends itself to interpersonal difficulties (Kornreich et al., 2002). Depression is also frequently found in chronic alcohol abusers (Zeigler et al., 2005).

Some CT studies have shown no differences between the brain hemispheres (Lee, Moller, Hardt, Haubek, & Jensen, 1985; Wilkinson &Carlen, 1979) while others describe more pronounced changes in the left hemisphere than the right (Gebhardt, Naeser, & Butters, 1984;

Golden et al., 1981). CT scans have also shown wider sulci in the cerebrum and enlarged ventricles suggestive of atrophy following prolonged alcohol use (Pfefferbaum, Rosenbloom, Crusan, and Jernigan, 1988). MRI studies reveal volume loss in the frontal lobes of chronic alcohol abusers (Pfefferbaum, Sullivan, Mathalon, & Lim, 1997). MRI studies have also revealed volumetric deficits in the extended reward and oversight center in the brain's right hemisphere (Makris et al., 2007). Some studies show greater right hippocampal atrophy in chronic alcohol abusers (Laakso et al., 2000), while other studies show greater volume loss of the left hippocampus (Beresford et al., 2006). Functional MRI (fMRI) has provided additional evidence of reduced activation in the amygdala and hippocampus of chronic alcohol abusers when presented with emotional words and expressions (Marinkovic et al., 2007).

Problem Statement

Traumatic brain injury is among the most prevalent causes of emergency department visits in the United States (Taylor, Bell, Breiding, & Xu, 2017). The psychological and neurocognitive impact of TBI extends far past the day of injury in which impairment can be seen for many months (Kinnunen et al., 2011). Alcohol abuse is known to negative effect brain structures as well as cognitive and psychological functioning (Zeigler et al., 2005). There is a large body of literature accounting for day-of-injury alcohol intoxication in the recovery of cognitive functioning following TBI. What is less clear is the impact that lifelong alcohol use has on neuropsychological functioning of older adults who have a history of moderate to severe traumatic brain injury.

Purpose Statement

The present study aimed to investigate the effects of alcohol abuse or dependence on the neuropsychological functioning of older adult Vietnam War veterans with a history of moderate

to severe TBI. The author hoped to identify impacted domains of functioning and the extent to which alcohol use exacerbates cognitive and psychological decline in individuals who have experienced a traumatic brain injury. Outcomes from the current study will better inform the trajectory of neuropsychological functioning in older adults who have a history of alcohol abuse and traumatic brain injury. Additionally, it will add perspective for which to interpret neuropsychological results in an older adult population. Furthermore, results from the present study can aid in treatment planning with a greater understanding of the likely capabilities and continued deficits of the older adult population.

Nature of the Study

The study design was quasi-experimental. Data was collected from the Alzheimer's Disease Neuroimaging Initiative Department of Defense (DOD-ADNI) dataset, which is available to individuals by an application and approval process. The study was comprised of three separate groups. One group was used as a control group and consisted of Vietnam War veterans who did not have a history of alcohol abuse and did not have a history of moderate or severe traumatic brain injury. Members of both experimental groups experienced at least one traumatic brain injury in which the skull was not penetrated. Additionally, one of the experimental groups was comprised of members who had a history of alcohol abuse and/or dependence, but they could not have been diagnosed with alcohol abuse or dependence within five years preceding the initial interview. The other group was comprised of individuals who did not have a history of alcohol abuse or dependence but had experienced at least one moderate to severe traumatic brain injury. Alcohol abuse and dependence were determined using the *Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Version IV* (SCID-IV; First, Spitzer, Gibbon, & Williams, 1996).

Inclusion and Exclusion Criteria

DOD-ADNI traumatic brain injury inclusion criteria. According to the DOD-ADNI protocol, individuals being considered for placement in the traumatic brain injury group must have met eligibility criteria. Each individual must be a veteran of the Vietnam War. They must be between 50 and 90 years of age at the time of enrollment. Each individual must have a moderate to severe non-penetrating TBI which occurred during military service in Vietnam, as confirmed by the Department of Defense or Veteran's Administration records. Additionally, all eligible individuals must live within 150 miles of the closest ADNI clinic in the subject's area. Moderate to severe TBI is identified in the study by (1) loss of consciousness, (2) post-traumatic amnesia greater than 24 hours, or (3) alterations of consciousness or mental state greater than 24 hours.

DOD-ADNI traumatic brain injury exclusion criteria. DOD-ADNI protocol manual outlined criteria in which individuals are considered not eligible for the study. If an individual is found to have mild cognitive impairment or dementia, they were no longer eligible for the study. Additionally, if a diagnosis of posttraumatic stress disorder (PTSD) was determined by either the SCID-IV or the Clinician Administered PTSD Scale (CAPS) score greater than 30, the individual was no longer considered eligible to be included in the database.

DOD-ADNI control group inclusion criteria. DOD-ADNI protocol manual set forth criteria that were met to qualify for the control group of the study. Each individual was a veteran of the Vietnam War. They must have been between the ages of 50 and 90 at the time of enrollment. The group needed to be comparable in terms of age, gender and, education with the traumatic brain injury group. The individual may be receiving disability from Veterans Affairs,

but the payments must not have been related to TBI or posttraumatic stress disorder (PTSD). Each individual must live within 150 miles of the closest ADNI clinic in the subject's area.

DOD-ADNI control group exclusion criteria. DOD-ADNI protocol manual detailed criteria which excluded individuals from being considered for the control group. Individuals must not have been diagnosed with mild cognitive impairment or dementia. Additionally, if a diagnosis of PTSD was determined by either the SCID-IV or a Clinician-Administered PTSD Scale (CAPS) score greater than 30, the individual was no longer considered eligible to be included in the database. Past and current PTSD was excluded. If the individual had a documented or self-reported history of TBI, they were no longer eligible for the control group. Furthermore, if an individual had experienced a head trauma which resulted in cognitive complaints, they were excluded from the control group. Additionally, if the individual had experienced a loss of consciousness greater than 5 minutes, they were not eligible for the control group.

DOD-ADNI exclusion criteria for all subjects. DOD-ADNI protocol manual outlined criteria which made subjects ineligible to participate in their study. If an individual had been diagnosed with mild cognitive impairment or dementia, they were not considered for the study. Also, if an individual had a history of psychosis or bipolar affective disorder, they were found to be ineligible. History of alcohol abuse or dependence within five years of study participation rendered the individual ineligible. MRI factors that made an individual ineligible included aneurysm clips, metal implants that are determined to be unsafe for MRI, and/or claustrophobia. Any individuals who were not appropriate for lumbar puncture, positron emission tomography (PET) scan or other procedures in the study were excluded. If an individual had experienced any major medical condition, the condition must have been stable for at least four months before the

individual was considered for the study. Examples of major medical conditions identified by DOD-ADNI included clinically significant hepatic, renal, pulmonary, metabolic or endocrine disease, cancer, HIV infection and AIDS, as well as cardiovascular disease. Cardiovascular diseases considered were cardiac surgery or myocardial infarction within four weeks before consideration, unstable angina, acute decompensated congestive heart failure or class IV heart failures, current significant cardiac arrhythmia or conduction disturbances, particularly those resulting in ventricular fibrillation or causing syncope, and high blood pressure. Additionally, individuals with any seizure disorder or other systemic illness affecting brain functioning during the five years before study enrollment were excluded, as were individuals with clinical evidence of stroke. Individuals with a relevant history of severe drug reactions or hypersensitivity to medications were not considered for the DOD-ADNI study. Finally, individuals with unstable medical comorbidities found upon record review or physical examination were excluded if it was determined that the comorbidity posed a safety risk to the individual.

In addition to the inclusion and exclusion criteria set forth by DOD-ADNI, the current study included additional criteria. Both current and/or prior history of PTSD were excluded from the current database. Additionally, only individuals who participated in the screening and baseline assessments were included. All individuals who were included in the database took part in the SCID-IV interview.

Research question

Will a group of older adult Vietnam War veterans with a history of alcohol abuse or dependence perform significantly worse on neuropsychological tests than individuals without a history of alcohol abuse if all individuals have experienced at least one moderate to severe traumatic brain injury? To what extent does alcohol abuse or dependence impact

neuropsychological functioning in older adults who have experienced at least one moderate to severe traumatic brain injury?

Hypotheses

Category Fluency Test. The group with a history of alcohol abuse or dependence will produce fewer words than the group with no history of alcohol abuse or dependence in one minute. To determine significant differences between groups, a one-way between-groups ANOVA will be performed with the allocated group as the factor and COWAT semantic fluency as the dependent variable.

Boston Naming Test. The group with a history of alcohol abuse or dependence will have a total score significantly less than those without a history of alcohol abuse or dependence. A one-way between-groups ANOVA will be performed with the allocated group as the factor and Boston Naming Test score as the dependent variable

Wechsler Memory Scale-Revised Logical Memory I. The group with a history of alcohol abuse or dependence will recall fewer details than the group with no history of alcohol abuse or dependence on Logical Memory I total score. A one-way between-groups ANOVA will be performed with the allocated group as the factor and WMS-R Logical Memory I score as the dependent variable.

Wechsler Memory Scale-Revised Logical Memory II. There will be no significant difference between the groups on the total score of logical memory II. A one-way between-groups ANOVA will be performed with the allocated group as the factor, and WMS-R Logical Memory II score as the dependent variable.

Rey Auditory Verbal Learning Test trial 6. There will be no difference between the groups on the number of words produced on RAVLT trial 6. A one-way between-groups ANOVA will be performed with the allocated group as the factor and RAVLT trials 1-6 score as the dependent variable.

Rey Auditory Verbal Learning Test trial 7. There will be no difference between the groups on the number of words produced on RAVLT trial 7. A one-way between-groups ANOVA will be performed with the allocated group as the factor and RAVLT trial 7 as the dependent variable.

Trailmaking Test A. There will be no difference between the groups on the speed in which it takes them to complete Trailmaking Test A. A one-way between-groups ANOVA will be performed with the allocated group as the factor and Trailmaking Test A time as the dependent variable.

Trailmaking Test B. The group with a history of alcohol abuse or dependence will complete Trailmaking Test B significantly slower than the group without a history of alcohol abuse or dependence. A one-way between-groups ANOVA will be performed with the allocated group as the factor and Trailmaking test B time as the dependent variable.

Geriatric Depression Scale. The group with a history of alcohol abuse or dependence will show significantly more depression than the group without a history of alcohol abuse or dependence. A one-way between-groups ANOVA will be performed with the allocated group as the factor and Geriatric Depression Scale score as the dependent variable.

CHAPTER II: REVIEW OF THE LITERATURE

The current chapter outlines key literature regarding the main components of this paper. It begins by highlighting the classification of traumatic brain injury and the different causes of damage to the brain. Structural and functional changes following a traumatic brain injury are discussed to provide insight into the vast realm of possible declines in neuropsychological functioning. The chapter then shifts its attention to the contributions of alcohol to changes in brain structure and functioning. The metabolism of alcohol and related neurochemistry are discussed before highlighting structural and functional expectations following prolonged alcohol use. The chapter then provides a brief outline of healthy aging with a specific focus on the cognitive functioning of healthy older adults. The chapter concludes by discussing the intersectionality of traumatic brain injury, alcohol, and healthy aging to provide a framework for the current study.

Traumatic Brain Injury

Definition of traumatic brain injury. The Center for Disease Control and Prevention defines TBI as "a bump, blow, or jolt to the head or a penetrating head injury that disrupts the normal function of the brain" (Binder, Corrigan, & Langlois, 2005; Faul, Xu, Wald, & Coronado, 2010). In accordance with the Center for Disease Control and Prevention definition of traumatic brain injury, disruption in normal brain functioning can be observed as any of the following clinical signs: 1) A period of loss of a decreased level of consciousness, 2) any loss of memory for events immediately before or after the injury, 3) neurological deficits such as weakness, loss of balance, change in vision, dyspraxia paresis/ plegia, sensory loss or aphasia, or 4) any alteration in mental state at the time of injury including confusion, disorientation, or slowed thinking (Menon, Schwab, Wright, & Maas, 2010).

Diagnostic criteria for traumatic brain injury. The most current diagnostic criteria can be found in the Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition (DSM-5; American Psychiatric Association, 2013, p. 624). The DSM-5 has outlined a set of criteria for the diagnosis of major or mild neurocognitive disorder resulting from TBI (American Psychiatric Association, 2013, p. 624):

1. The criteria are met for major or mild neurocognitive disorder.
2. There is evidence of a traumatic brain injury—that is, an impact to the head or other mechanisms of rapid movement or displacement of the brain within the skull, with one or more of the following:
    a. Loss of consciousness.
    b. Posttraumatic amnesia.
    c. Disorientation and confusion.
    d. Neurological signs (e.g., neuroimaging demonstrating injury; new onset of seizures; a marked worsening of a preexisting seizure disorder; visual field cuts; anosmia; hemiparesis).
3. The neurocognitive disorder presents immediately after the occurrence of the traumatic brain injury or immediately after recovery of consciousness and persists past the acute post-injury period.

Classification of traumatic brain injury. The Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) is a widely accepted measure of TBI severity. The scale includes points that range from 3-15 and provides information about an individual's level of consciousness and cognitive functioning (Teasdale & Jennett, 1974). The GCS scores are based on the best motor response, best verbal response, and opening of the eyes. TBI can be classified into mild, moderate, and

severe depending on mental status and level of consciousness (LOC). Mild TBI is classified as a GCS score of 13-15. An individual experiencing mild TBI would be conscious and be able to respond to verbal communication but may not be able to localize painful stimuli. Moderate TBI has a GCS score between 9-12. An individual who has experienced a moderate TBI would likely still be conscious but may appear disoriented and have difficulty communicating verbally. Severe TBI has a GCS score between 3 and 8. Generally, patients designated with the severe classification have a complete loss of consciousness, unable to verbally communicate, and/or are unable to open their eyes. Another system used to determine TBI severity is The Mayo Classification System (Malec et al., 2007). The Mayo Classification System for TBI severity separates classifications by definite moderate-severe (definite) TBI, mild (probable) TBI, and symptomatic (possible) TBI (Malec et al., 2007). Definite moderate-severe TBI includes death as a direct result of the TBI, loss of consciousness greater than 30 minutes, posttraumatic amnesia longer than 24 hours, or achieving a GCS score within 24 hours of less than 13 (Malec et al., 2007). Probable mild TBI must include either loss of consciousness less than 30 minutes or posttraumatic amnesia is present but lasts for less than 24 hours (Malec et al., 2007). Possible TBI is classified as having one of the following symptoms: headache or nausea, blurred vision, dazed, dizziness, confusion, or focal neurological symptoms (Malec et al., 2007). Additionally, the Defense and Veteran's Brain Injury Center (2016) has developed a classification system to aid in the categorization of TBI. A traumatic brain injury is classified as either (1) concussion/ mild TBI, (2) moderate TBI, (3) Severe TBI, or (4) penetrating TBI/open head injury. Distinctions are made according to state of consciousness, memory loss, and structural brain imaging. A penetrating head injury is confirmed if the scalp, skull, and dura mater are penetrated.

Additionally, post-traumatic amnesia (PTA) is utilized as an additional index of TBI severity (Nakase-Richardson et al., 2011). PTA is the time from the original injury until the individual is oriented and able to form new memories and recall them. In terms of TBI severity, a moderate classification is designated when PTA is from 1-24 hours, but some extend the moderate designation beyond 24 hours (Mild Traumatic Brain Injury Committee, 1993). Individuals who are experiencing post-traumatic amnesia may experience symptoms such as perceptual disturbances, changes in the sleep-wake cycle, agitation, and variable effect (Nakase-Richardson, Yablon, & Sherer, 2007).

Etiology of traumatic brain injury. The damage during a TBI can be thought of as resulting in multiple stages. The primary injury occurs at the time of the original injury while the secondary injury has a delayed clinical presentation and is not mechanically induced (Werner & Engelhard, 2007).

Primary injury. The initial phase of the injury can be caused by direct trauma as well as acceleration and deceleration of the brain and rotational forces (Werner & Engelhard, 2007). The primary insult can be diffuse, focal, or both. Four of the primary insults seen during the initial injury phase include skull fractures, contusions, intracranial hemorrhages, and diffuse axonal injury (Martin & Johnstone, 2005). In closed head injuries, the main damage observed following the primary phase of the injury is largely tissue damage (Gentry, 1994) and also encompasses mechanical damage to neurons, axons, glia, and blood vessels as a result of stretching, tearing, or shearing (Saatman et al., 2008). Linear skull fractures result in a break of a single line which commonly results from falls and is considered to be the most common type of skull fracture (Hardman & Manoukian, 2002). Depressed skull fractures result in bone fragments being propelled inward, usually occurring in frontal and parietal areas of the skull (Hardman &

Manoukian, 2002). Cortical contusions are frequently found on gyri at the brain's surface as a result of acceleration-deceleration forces (Burke & Ordia, 2000). Cortical contusions to the orbitofrontal and anterotemporal regions are commonly seen during the initial injury phase and are associated with subarachnoid hemorrhage (Greenwald, Burnett, & Miller, 2003). The specific location of the contusions is these regions can be attributed to the coup-countrecoup movement of the brain (Ferrell & Tanev, 2002) as well as the protrusion of bone at the orbital surface of the frontal lobes and temporal tips (Martin & Johnstone, 2005). Intracranial hemorrhages most commonly lead to death in individuals who are coherent immediately following injury (Greenwald, Burnett, & Miller, 2003) due to the pressure exerted on brain structures with the skull (Martin & Johnstone, 2005). Chronic subdural hematomas, forming weeks after an event, are most common in older adults (Karnath, 2004). Diffuse axonal injury (DAI) is common in the initial injury phase with 40% to 50% of TBI hospital admissions having DAI pathology (Meythaler, Peduzzi, Eleftheriou, &Novack, 2001). DAIs are primarily caused by acceleration-deceleration and rotational forces which shear the axons (Greenwald, Burnett, & Miller, 2003). Significant DAI may be commonly found accompanying loss of consciousness or coma (McAllister, 1992).

Secondary injury. The secondary injury occurs with the biomolecular and physiological changes that arise following the primary method of injury (Greve & Zink, 2009). The damage from secondary injury can be caused by cascading metabolic, biochemical, and cellular (Loane & Faden, 2010) processes leading to elevated intracranial pressure and a reduction in cerebral blood flow (Greve & Zink, 2009). Increased intracranial pressure may lead to hypoxia, ischemia, hemorrhage and herniation as well as cell death as a result of necrosis or apoptosis (Loane & Faden, 2010). A variety of processes account for secondary injury mechanisms including

depolarization, disturbances of ionic homeostasis, release of neurotransmitters such as glutamate, lipid degradation, mitochondrial dysfunction, and initiation of inflammatory and immune processes (Loane & Faden, 2010). Biochemical events of the secondary injury produce toxic and pro-inflammatory molecules which can lead to lipid peroxidation, edema, and disruption of the blood-brain barrier (Loane & Faden, 2010). Additionally, glutamate activates N-methyl-D-asparate (NMDA) and amino-3-hydroxl-5-methyl-4-isoxazolepropionate (AMPA) receptors which increase the neuronal influx of calcium and sodium (Greenwald, Burnett, & Miller, 2003). The energy reserves are depleted in an attempt to reestablish the sodium-potassium gradient. Free radicals and oxidants continue to degrade neuronal cell membranes which perpetuates the cycle of glutamate release (Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). Posttraumatic epilepsy is a common occurrence during the secondary injury phase is often unresponsive to medical intervention (Semah et al., 1998). Posttraumatic epilepsy occurs in approximately 5%-19% of the civilian population (Bushnik, Englander, & Duong, 2004; Englander et al., 2003).

Brain mechanisms following traumatic brain injury.

Cellular changes. Many interactions are happening at the cellular level leading to eventual cell death. Ischemic cascade leads to the release of free radicals, which breaks down neuronal membranes triggering an inflammatory response (Graham et al., 1989). Cell damage and necrosis occur following a TBI due to an influx of calcium released into the neurons and other cells following the release of glutamate, which results in oxygen radical reactions (Greve & Zink, 2009). Glutamate release is considered to be a significant contributing factor during the neuroexcitation phase (Yoshino, Hovda, Kawamata, Katayama, & Becker, 1992; Hovda, 1996). The cell then becomes unstable due to high calcium concentrations and the presence of free-radical molecules (Greve & Zink, 2009). The unstable environment triggers increased production

of nitric oxide and glutamate which are subsequently released (Greve & Zink, 2009). Each of the three components that are released in the cell has excitatory potential for the other two components, resulting in neuronal apoptosis (Greve & Zink, 2009). Microglia activate as an anti-inflammatory response releasing pro- and anti-inflammatory cytokines and chemokines which modulate secondary injury as well as neuronal recovery following injury (Smith, 2013; Loane & Byrnes, 2010). The response of microglia following injury includes phagocytosis, scavenging of debris, angiogenesis, and healing of the wound (Witchner, Eiferman, & Godbout, 2015). Evidence suggests that microglia play a role in minimizing neuronal death following TBI (Witchner, Eiferman, & Godbout, 2015).

Gray matter changes. Gray matter is most often damaged by linear forces causing contusions or hemorrhages to cortical regions (Blumbergs et al., 1994). The most vulnerable regions of the brain during a traumatic event are the frontal and temporal regions where cortical gray matter is exposed to bony ridges on the inside of the skull (Genarelli & Grabau, 1998). Thinning of gray matter has been observed in the anterior cingulate cortex, ventromedial and dorsolateral prefrontal cortex, and motor cortex in postmortem examination of injured brains (Maxwell, MacKinnon, Stewart, & Graham, 2010). One study found the presence of DAI contributed to more significant cortical thinning when compared to controls (Maxwell, MacKinnon, Stewart, & Graham, 2010). Analysis of hippocampal volume revealed approximately 20% less volume in the right hippocampus when compared to the left hippocampus in veterans with TBI following blast exposure which was associated with reduced visual memory (De Lanerolle, et al., 2014).

White matter changes. Rotational components of a TBI are believed to result in deeper cerebral lesion (McLean, 1996). Rotational forces cause shear damage to the white matter tracts,

known as diffuse axonal injury (DAI; Thibault & Gennarelli, 1990). DAI is characterized by the stretching of axons, and the disruption and tearing of nerve fibers (Adams, Graham, Murray, & Scott, 1982). Currently, the identification of DAI can only be accomplished microscopically (De Lanerolle, Kim, & Bandak, 2015). DAI is classified into three grades. Grade one DAI is characterized by white matter changes in the cerebral cortex, brainstem, corpus callosum, and cerebellum (De Lanerolle, Kim, & Bandak, 2015; Adams, Doyle, Ford, Gennarelli, Graham, & Mclellan, 1989). Grade two of DAI encompasses grade one criteria with additional focal lesions of the corpus callosum (De Lanerolle, Kim, & Bandak, 2015; Adams, Doyle, Ford, Gennarelli, Graham, & Mclellan, 1989). A grade three DAI consists of criteria from grades one and two with additional focal lesions in the dorsolateral quadrants of the anterior brain stem (De Lanerolle, Kim, & Bandak, 2015; Adams, Doyle, Ford, Gennarelli, Graham, & Mclellan, 1989). The occurrence of mTBI has been shown to result in the accumulation of hyperphosphorylated tau (p-tau) as neurofibrillary tangles and neurites (McKee & Robinson, 2014). Additionally, myelinated fiber loss and axonal degeneration have been found in military members following blast exposure (McKee & Robinson, 2014).

The blood-brain barrier. The blood-brain barrier is a semipermeable membrane barrier that acts as a barricade between the vascular system and the brain and the extracellular fluid of the central nervous system. The blood-brain barrier is responsible for mediating the chemical environment of the brain by allowing the passage of ions, nutrients, and peptides into the brain (Singh, Jiang, Gupta, & Benlhabib, 2007). The blood-brain-barrier has been shown to break down following a traumatic brain injury (Chodobski, Zink, & Szmydynger-Chodobska, 2011). Blocking of the oxidative degradation of lipids likely reduces the permeability of the blood-brain-barrier following a traumatic brain injury (Smith, Andrus, Zhang, & Hall, 1994). There is

evidence that damage to the blood-brain barrier also occurs as a result of microhemorrhages, astrocytosis, and activated clusters of microglia surrounding vascular structures following TBI (McKee, Daneshvar, Alvarez, & Stein 2014). Free radicals are not only responsible for the detrimental effects on glial cells and neurons, but they also induce damage to the blood-brain-barrier, the brain's primary mechanism for vascular filtration (Smith, Andrus, Zhang, & Hall, 1994).

Imaging following traumatic brain injury.

There are a variety of methods used when assessing the extent of structural damage to the brain. Some of the techniques aim to detect large lesions and cortical volume loss while others are used primarily to detect damage to white matter.

Computed tomography. Computed tomography (CT) is an imaging technique that uses computer-assisted X-rays to create three-dimensional renderings of an internal structure (Brenner & Hall, 2007). CT is the imaging modality of choice during the acute phase of injury (Mass, Hukkelhoven, Marshall, & Steyerberg, 2005) but is less sensitive to mTBI in which negative CT scans are not uncommon during the 24 hours immediately following an injury (Bigler & Maxwell, 2012). However, during later stages of injury, MRI is more effective in detecting small white matter lesions (Uchino, Okimura, Tanaka, Saeki, & Yamaura, 2001; Firsching et al., 2001). The advantage of CT is its ability to quickly and accurately identify intracranial hemorrhaging (Kim & Gean, 2011). CT scans of an injured brain may reveal abnormalities such as petechial hemorrhages, subarachnoid hemorrhages, or evidence of contusion (American Psychiatric Association, 2013).

Magnetic resonance imaging. Magnetic Resonance Imaging (MRI) uses a strong magnet to form a structural image of the brain by recording the excitation of protons in the body (Mori &

Barker, 2002). MRI can detect nonhemorrhagic damage such as cortical contusions and traumatic axonal injuries (Kim & Gean, 2011). The use of gradient-echo imaging allows for the identification of hyperintensities suggestive of microbleeds (Kinnunen et al., 2011) which are an indication of diffuse axonal injury (Schneid, Preul, Gruber, Wiggins, & Von Cramon, 2003). The utility of MRI comes in the subacute and chronic phases of TBI in which differing contrasts can provide input into secondary damage (Gallagher, Hutchinson, & Pickard, 2007; Aquino, Woolen, and Steenberg, 2015). Functional MRI (fMRI) during a computerized cognitive test battery showed reduced activation in the dorsolateral prefrontal cortex in individuals with mild and moderate levels of post-concussion symptoms (Chen, Johnston, Collie, McCrory, & Ptito, 2007).

Diffuse tensor imaging. Diffuse Tensor Imaging (DTI) assesses the directional orientation and coherence of myelin of white matter tracts by evaluating the magnitude and orientation of water movement through each voxel in a tissue (Mori & Zhang, 2006). Commonly derived data from DTI are fractional anisotropy (FA) and mean diffusivity (MD). FA and MD give information about the microstructural organization and diffusivity of water in tissue (Le Bihan, 2003). Higher FA values indicate more intact tissue structure while higher MD values indicate damage to the tissue (Rugg-Gunn, Symms, Barker, Greenwood, & Duncan, 2001; Arfanakis et al., 2002). Lower FA was found to be associated with the loss of myelinated axons (Laitinen, Sierra, Bolkvadze, Pitkanen, and Grohn, 2015). DTI can show changes in white matter integrity and alternations in fiber tracts which are not readily seen with structural imaging techniques such as CT and MRI (McKee & Robinson, 2014). Following a TBI due to blast, DTI shows lower FA and higher MD (Taber et al., 2014; MacDonald et al., 2011) in the corpus callosum (Peskind et al., 2011).

Changes in neuropsychological functioning. Traumatic brain injuries can cause extensive and lasting effects in a variety of domains of neuropsychological functioning. The extent of cognitive sequelae following TBI can be attributed to factors such as TBI severity, complications following TBI, associated injuries to other parts of the body, and chronicity of the injury (Rabinowitz & Levin, 2014).

General intelligence. Individuals with mild closed head injury performed significantly worse than healthy controls on a measure of general intelligence (Bassett & Slater, 1989). In the sub-acute phase, full-scale IQ deficits were found to be minimal for mild and moderate TBI, but large deficits were noted in patients following a severe TBI (Konigs, Engenhorst, & Oosterlaan, 2015). Post-acute individuals also showed significantly lower general intelligence than healthy controls with lower verbal and nonverbal abilities (Kinnunen et al., 2011). Verbal IQ was found to be significantly lower than controls in individuals who experienced a TBI (Bassett & Slater, 1990; Kinnunen et al., 2011). Factors such as scores on the Glasgow Coma Scale and posttraumatic amnesia duration appeared to at least moderately predict outcomes on full-scale IQ, performance IQ, and verbal IQ (Konigs, Engenhorst, & Oosterlaan, 2015).

Executive functioning. Executive functioning is a commonly cited deficit following traumatic brain injury. Central to the control of executive functioning are the prefrontal cortex (Miller, 2000; Levin, Eisenberg, & Benton, 1991; Struss and Benson, 1986) and the communication between the frontal and posterior brain regions (Barbey et al., 2012; Koenigs, Barbey, Postle, & Graftman, 2009). Areas of functioning commonly impacted include planning (Shum et al., 2009; Levin & Kraus, 1994; Miller, 2000), judgment, and cognitive aspects of decision making (Rabinowitz & Levin, 2014). Individuals with a TBI are more likely to violate rules and take extra steps to complete a task (Shum et al., 2009) than individuals without TBI.

Deficits in judgment and decision making are more likely to be impacted in individuals with moderate to severe TBI (Levin et al., 2010). DTI revealed that correlations exist between decision-making deficits and abnormalities in subcortical structures such as the thalamus, dorsal striatum, and caudate (Newcombe et al., 2011). Impulsivity correlates were found by DTI to involve bilateral orbital frontal gyri, caudate, and insula (Newcombe et al., 2011). Rational decision-making impairments were associated with abnormalities in the dorsolateral prefrontal cortex, the superior frontal gyri, and the right ventromedial prefrontal cortex, hippocampus, and ventral striatum (Newcombe et al., 2011). Phonemic fluency is significantly diminished following mTBI when compared to healthy controls (Mangels, Craik, Levine, Schwarts, and Stuss, 2002; Kinnunen et al., 2011) and matched the performance of the severe TBI group (Bassett & Slater, 1990). Impairments in set shifting (Kinnunen et al., 2011), planning, and the use of strategies were found in TBI patients when compared to healthy controls (Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009; Frencham, Fox, and Mayberry, 2005). Impairments in set shifting were also found to be associated with higher mean diffusivity, specifically in the superior frontal white matter (Kinnunen et al., 2011). Behavioral initiation may also be diminished following TBI (van Reekum, Stuss, & Ostrander, 2005). Subcortical lesions and right hemispheric dysfunction is believed to contribute to behavioral initiation difficulties (Andersson, Krogstad, & Finset, 1999).

Attention and working memory. There is a dose-response relationship in which the severity of the injury is correlated with the amount of impairment seen (Carlozzzi, Grech, & Tulsky, 2013). Working memory deficits have been noted following closed head TBI which is attributed to focal injury of the dorsolateral prefrontal cortex (Rabinowitz & Levin, 2014). Top-down control of attention is negatively impacted following a TBI (Dockree et al., 2005). Divided

attention at the memory encoding phase was associated with lower recall ability (Mangels, Craik, Levine, Schwartz, & Stuss, 2002). Sustained attention has also been shown to be diminished in individuals following TBI (Chan, 2005; Vanderploeg, Curtiss, & Belanger, 2005; Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009; Ponsford & Kinsella, 1992). Working memory was shown to be significantly worse for participants with TBI, especially in individuals with post-concussive symptoms (Dean & Sterr, 2013).

Processing speed. On a task of speeded visual tracking, one study (Bassett & Slater, 1990) found that the mTBI group did not perform significantly worse than the healthy control group, but completion time was significantly slower in the group of individuals with severe TBI. Alternatively, others found significantly slower visual tracking in the TBI group when compared to healthy controls (Kinnunen et al., 2011), especially in participants who were experiencing post-concussive symptoms (Dean & Sterr, 2013). Speeded color naming was also significantly slower in individuals with a history of TBI when compared to healthy controls (Kinnunen et al., 2011). Slowed processing speed was found to be a contributing factor in observed attentional deficits (Ponsford & Kinsella, 1992). When accounting for practice effects on a measure of attention, participants with TBI performed worse than controls indicating that the TBI group was slower to regain the ability to process information that was presented rapidly (O'Jile et al., 2006).

Memory. Specific memory tasks impacted by TBI include memory acquisition and retrieval rather than memory storage (Dikmen et al., 2009; Stuss & Alexander, 2000). Verbal memory for stories did not show a significant decline in participants with mTBI, but was significantly lower for participants with severe TBI (Bassett & Slater, 1990). Visual recognition was relatively spared one year after injury (Levin et al., 2009). A likely explanation for the discrepancy between verbal and visual memory deficits is the known contribution that PTSD

symptoms have on visual memory (Levin et al., 2009; Vanderploeg, Belanger, & Curtiss, 2009). Visual memory for the reproduction of figures in a group of mTBI patients did not significantly differ from healthy control groups in immediate or delayed recall (Bassett & Slater, 1990). Immediate associational memory was significantly worse following TBI than healthy controls (Kinnunen et al., 2011). The structure of the fornices was found to be predictive of associational memory functioning with more anisotropic white matter predicting better performance (Kinnunen et al., 2011; Kessler et al., 2001). Hippocampal damage has also been indicative of memory impairment (Tate & Biggler, 2000).

Emotion, affect, and personality. Considerations must be made for associated symptomology when evaluating the outcome of TBI. Specifically, with regard to military personnel who have experienced blast-related traumatic brain injury in the OIF/OEF engagements, it is not uncommon to observe evidence of post-concussion symptoms (PCS) and PTSD symptoms (Hoge et al., 2008; Levin et al., 2009; Schneiderman, Braver, & Kang, 2008). PTSD and PCS share many common attributes that make distinguishing between the two difficult for clinicians (Stein & McAllister, 2009). Both PTSD and PCS show signs of depression, anxiety, insomnia, irritability or anger, difficulty concentrating, fatigue, hyperarousal, and/or avoidance (Stein & McAllister, 2009). Unique to PTSD are symptoms such as re-experiencing a traumatic event, shame, and guilt (Stein & McAllister, 2009). Unique to PCS are symptoms such as headaches, sensitivity to light and sound, memory deficits, and dizziness (Stein & McAllister, 2009). Executive functioning involves behavioral components that show dysfunction which is not captured by cognitive domains. Emotional aspects of decision making, motivation, and impulsivity have been known to be disrupted following traumatic brain injury (Rabinowitz & Levin, 2014). Emotional regulation difficulties have been noted following

TBI (Erez, Rothschild, Katz, Tuchner, & Hartman-Maeir, 2009) with depression having a prevalence rate of 44.3% (Van Reekum, Cohen, & Wong, 2000). In contrast to cognitive functioning impacted by TBI, psychological effects following TBI were not correlated with the severity of injury (Rassovsky et al., 2006).

Recovery following traumatic brain injury. The severity of the injury is a great indicator of the amount of cognitive impairment expected to be experienced. Moderate to severe TBI has been shown to lead to more substantial and more persistent cognitive impairment than mild TBI (Rassovsky et al., 2006; Schretlen & Shapiro, 2003). It is possible, however, to show cognitive recovery following traumatic brain injury (Binder, 1997; Schretlen & Shapiro, 2003). Approximately 80% to 90% of individuals who have experienced mTBI make a favorable recovery of cognitive symptoms (Binder, 1997). Individuals with mTBI recover cognitive functioning comparable to healthy peers around 3 months post-injury (Schretlen & Shapiro, 2003). The same recovery rates have not been found for individuals who have experienced a moderate to severe TBI (Schretlen & Shapiro, 2003). Recovery rates following a moderate-severe TBI are variable and can be influenced by age, race, and availability of post-acute care (Howrey et al., 2017). Most improvements in functioning occur within the first six months following the injury (Sandler, 2002). Between six months and two years following the injury, some improvements can occur but at a much slower rate (Sandler, 2002). After two years, recovery generally levels off and change can be a result of compensatory strategies (Sandler, 2002).

Alcohol

Alcohol is classified as a central nervous system depressant, similar to sedative-barbiturates, benzodiazepines, and morphine (Winger, Hofman, & Woods, 1992). The effects of excess alcohol ingestions can cause intoxication (Parsons, 1996).

Alcohol metabolism. The metabolic process of alcohol is similar to the process for other nutrients. After ingested, alcohol is exposed to the process of first-pass metabolism (Crabb, Matsumoto, Chang, & You, 2004). First-pass metabolism is important so that the entirety of the drug does not reach the target organ. First-pass metabolism occurs within the gastrointestinal tract as well as the liver, but the proportion that each is responsible for is heavily debated (Brown, Fiatarone, Kelly, Day, & James, 1995; Yin et al., 1997). It is estimated that first-pass metabolism is responsible for approximately 8-9% of total alcohol metabolism, with approximately 6% occurring in the gastrointestinal tract (Ammon, Schäfer, Hofmann, & Klotz, 1996). Once ethanol is absorbed and passes through the liver, the remaining ethanol is distributed into the body water space where it becomes metabolized in the liver by alcohol dehydrogenase in the cytosol and cytochrome P450-2E1 in micromes and becomes acetaldehyde (Crabb, Matsumoto, Chang, & You, 2004). The conversion of ethanol to acetaldehyde can cause acetaldehyde to bind to proteins (Nakamura et al., 2003), nucleic acids (Wang et al., 2000), and phospholipids (Trudell, Ardies, & Anderson, 1990). The binding caused by oxidation of acetaldehyde disrupts the functioning of cellular components (Deitrich, Zimatkin, & Pronko, 2006). Acetaldehyde is then converted to acetate by aldehyde dehydrogenases (Crabb, Matsumoto, Chang, & You, 2004). The acetate is then consumed by the brain taking the place of the glucose metabolic process that occurs in the absence of acetate (Learn et al., 2003; Pawlosky et al., 2010; Volkow et al., 2006). Acetate is then further broken down into carbon dioxide and

water which are more easily eliminated from the body (National Institute on Alcohol Abuse and Alcoholism, 1997).

Neurotransmitters. In a healthy brain, there is a balance of inhibitory and excitatory neurotransmitters (Valenzuela, 1997). In short term alcohol use, alcohol potentiates the major inhibitory neurotransmitter in the brain, gamma-aminobutyric acid (GABA) through the $GABA_A$ receptor subtype (Valenzuela, 1997; Zeigler et al., 2005). The same $GABA_A$ receptor is responsible for the sedative effects of benzodiazepines (Valenzuela, 1997). Alcohol also appears to activate the neuromodulator adenosine system which can lead to sedation (Valenzuela, 1997). Alcohol use also reduces excitatory neurotransmission by inhibiting aspartate and glutamate, the major excitatory neurotransmitter in the brain (Zeigler et al., 2005). Aspartate and glutamate act through NMDA and non-NMDA receptors which, when inhibited can result in sedation (Valenzuela & Harris, 1997). To compensate for the inhibited excitatory neurotransmitters and increase in inhibitory neurotransmitter activity in longer-term alcohol use, the brain attempts to achieve equilibrium by increasing excitatory neurotransmitter activity in glutamate while decreasing inhibitory neurotransmission in $GABA_A$ (Mihic & Harris, 1995; Valenzuela & Harris, 1997). Due to changes in the protein composition of $GABA_A$ receptors, sensitivity to neurotransmission is decreased (Valenzuela, 1997). Additionally, glutamate appears to compensate by increasing excitatory activity (Tabakoff & Hoffman, 1996; Valenzuela & Harris, 1997). Once alcohol is no longer a factor in the brain, NMDA receptors are disinhibited, leading to larger than normal NMDA receptor activity (Gonzales & Jaworski, 1997). As a result of increased activity in excitatory neurotransmission, excitotoxicity occurs leading to cell death and loss of neurons (Tsai et al., 1995).

Glucose metabolism. Glucose acts as the primary source of the brain's energy (Handa, DeJoseph, Singh, Hawkins, & Singh, 2000). During alcohol intoxication, the brain metabolism of glucose slows in favor of an increase in the rate of acetate metabolism as a primary source of energy (Volkow et al., 2015). Specifically, glucose phosphorylation is reduced in cortical and cerebellar regions when alcohol is present, but it generally does not affect the basal ganglia or corpus callosum (Schreckenberger et al., 2004; Volkow et al., 1990). The decreased rate of glucose metabolism during intoxication was found to be more pronounced in heavy drinkers as opposed to healthy individuals (Volkow et al., 1995). In essence, with a lack of glucose metabolism, the brain is slower to gather the necessary energy to perform functions of a designated region (Volkow et al., 2015). Studies have shown a decrease in the rate of glucose metabolism in the frontal cortex of chronic alcohol abusers which increases during alcohol withdrawal periods (Muneer, Alikunja, Szlachetka, & Haorah, 2011). It is hypothesized that repeated intoxication and withdrawal promotes neuronal injury due to the excitotoxicity of glutamate-mediated by the upregulation of N-methyl-D-asparate (NMDA) receptors which play a role in long-term potentiation (Sachdeva, Chandra, Choudhary, Dayal, & Anand, 2016). Excitotoxicity leads to increased calcium levels within the cell which mediates oxidative stress and the loss of cholinergic muscarinic receptors (Sachdeva, Chandra, Choudhary, Dayal, & Anand, 2016). Impaired utilization of glucose as a result of blood-brain-barrier dysfunction leads to neurotoxicity and loss of neurons in the brain (Muneer, Alikunja, Szlachetka, & Haorah, 2011).

Effects on the blood-brain-barrier. The blood-brain-barrier is comprised of brain microvascular endothelial cells, pericytes, and astrocytes (Rubin & Staddon, 1999). The blood-brain-barrier is responsible for allowing ions, molecules, and leukocytes to move in or out of the

brain (Hawkins & Davis, 2005). Tight junctions are responsible for the integrity of the blood-brain-barrier (Pardridge, 1983). Intracellular calcium signaling and the phosphorylation of tight junction proteins contribute to impairments in the blood-brain-barrier (Hawkins & Davis, 2005). Alcohol has been shown to increase the permeability of the blood-brain-barrier after short- and long-term exposure by disrupting the endothelial tight junctions (Haorah et al., 2005a). Alcohol has also been shown to increase the expression of alcohol-metabolizing enzymes, cytochrome P450-2E1, and alcohol dehydrogenase in the brain microvascular endothelial cells (Haorah et al., 2005a). The metabolism of alcohol produces acetaldehyde and reactive oxygen species, decreasing the integrity of the brain microvascular endothelial cells by oxidative stress (Haorah et al., 2005b).

Cellular changes.

***Gray matter changes*.** Functional imaging studies have shown activation of multiple brain regions when alcohol-dependent individuals are exposed to alcohol-associated cues. Areas of activation with alcohol-related stimuli include: the orbitofrontal cortex (OFC; Myrick et al., 2004; Wrase et al., 2002); the medial prefrontal cortex (MPFC) and the adjacent anterior cingulate cortex (ACC); Grüsser et al., 2004; Myrick et al., 2004; Kareken et al., 2010; Tapert, Brown, Baratta, & Brown, 2004); and the ventral and central striatum, including the nucleus accumbens (Wrase et al., 2002; Braus et al., 2001; Myrick et al., 2008; Vollstädt-Klein et al., 2010; Wrase et al., 2007) and the basolateral amygdala (Schnieder et al., 2001). Neuroimaging has confirmed that excessive alcohol abuse leads to both structural and functional changes (Bates, Bowden, & Barry, 2002; Harper, 2009). Alcohol-related structural changes have been observed in the prefrontal cortex, cingulate cortex, amygdala, hippocampus, and cerebellum (Wodbrock et al., 2009). The frontal lobes have been consistently shown to be particularly

vulnerable to chronic alcohol abuse when compared to other cerebral locations (Dirksen, Howard, Cronin-Golomb, & Oscar-Berman, 2006; Gansler et al., 2000; Ratti, Bo, Giardini, & Soragna, 2002). Neuronal density is decreased in the prefrontal cortex of chronic alcohol users in postmortem studies (Harper & Matsumoto, 2005). Prolonged chronic alcohol abuse disrupts the blood flow to the brain and causes alterations in the metabolic processes and atrophy in the brain (Nicolas et al., 1993; Volkow et al., 2002). However, the brain can regain blood flow to the frontal lobes (Johnson-Greene et al., 1997) and cerebellum (Ende et al., 2005; Seitz et al., 1999), with a return to approximately normal blood flow after 4 years of abstinence (Gansler et al., 2000). Damage to the mammillary bodies of the hypothalamus are common in chronic alcohol abusers and have been implicated in the resulting memory dysfunction (Oscar-Berman & Marinkovic, 2007).

***White matter changes*.** Binge drinking in adolescents aged 16-19 has been associated with decreased fractional anisotropy due to compromised white matter fiber coherence in frontal, temporal, parietal, and cerebellar regions (McQueeney et al., 2009). Postmortem structural MRI has found that prolonged alcohol abuse has profound adverse effects on cerebral white matter (Lewohl et al., 2000). Postmortem RNA analysis of superior frontal structures confirmed that gene structures responsible for myelination were downregulated in individuals with alcohol abuse (Lewohl et al., 2000). Significant volume reduction has also been found in cortical and subcortical regions associated with reward circuitry in long-term alcohol-abusing patients who have recently become abstinent (Makris et al., 2008). Additional damage has been found in the microstructural makeup up the right hemisphere. Trivedi et al., (2013) found that white matter fiber tracts were more significantly damaged in the right hemisphere of the reward system in chronic alcoholics when compared to the left hemisphere. The same study also found reduced

fractional anisotropy in the corpus callosum, fornix, arcuate fasciculus of the right hemisphere, and right inferior longitudinal fasciculus when compared to healthy controls. DTI studies have shown white matter damage in chronic alcohol abusers in the corpus callosum (Liu et al., 2010), centrum semiovale (Pfefferbaum & Sullivan, 2002; Pfefferbaum & Sullivan, 2005; Pfefferbaum et al., 2000; Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007), as well as widespread FA deficits in both hemispheres (Pfefferbaum, Adalsteinsson, & Sullivan, 2006). White matter tracts connecting prefrontal and limbic systems have also been found to be deficient in alcohol-abusing men (Harris et al., 2008). The frontal association cortex and hypothalamus have also been found to experience neuronal loss following alcohol abuse (Harper, 2009; Harper & Matsumoto, 2009). Prolonged abstinence can reverse the shrinkage of white matter that occurred during prolonged alcohol abuse (Bartsch et al., 2007; Sullivan and Pfefferbaum, 2005).

Neuropsychological functioning. Chronic alcohol abuse can have long-lasting negative consequences ranging from mild cognitive impairment to dementia (de la Monte & Kril, 2014). Unlike Alzheimer's disease, alcohol-related cognitive impairment is frequently seen in middle-aged individuals (Matsui, Sakurai, Toyama, Yoshimura, Matsushita, & Higuchi, 2012). Wernicke's encephalopathy is a neuropsychiatric disorder characterized by altered mental state, ataxia, and weakening of the eye muscles which is caused by vitamin B1 (thiamine) deficiency (de la Monte & Kril, 2014). Wernicke's encephalopathy is a result of inadequate nutritional intake by the alcohol abuser as well as the inhibition of thiamine absorption in the gastrointestinal tract and the activation of thiamine via phosphorylation (Todd, Hazell, & Butterworth, 1999). If Wernicke's encephalopathy goes untreated and alcohol abuse is present, it can develop into a chronic neuropsychiatric condition known as Korsakoff syndrome (de la Monte & Kril, 2014). Korsakoff syndrome is characterized by deficits in memory formation and

executive functioning due to neuronal damage of the thalamus, frontal lobes, mammillary bodies, cerebellum, and hippocampus (Jung, Chanraud, & Sullivan, 2012). While some research suggests long-term effects of chronic alcohol abuse, other research has shown that neurocognitive recovery in most domains is possible following prolonged abstinence. In one particular study, individuals with approximately 6 years of abstinence from alcohol performed identically to controls in all domains except spatial processing (Fein, Torres, Price, & Di Sclafani, 2006).

Hypotheses of neuropsychological changes. There is disagreement amongst experts on whether the effects of alcohol abuse are diffuse in nature or if specific cognitive functions are affected. The frontal lobe hypothesis posits that the anterior regions of the brain are most affected by alcohol abuse (Ellis & Oscar-Berman, 1989, Jones & Parsons, 1971; Oscar-Berman & Schendan, 2000; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003). In contrast to the diffused brain dysfunction hypothesis, the frontal lobe hypothesis has been argued for primarily due to common impairments in alcohol-abusing individuals such as impaired inhibition, cognitive flexibility, organization, and planning (Ambrose, Bowden, & Whelan, 2001; Demir, Uluğ, Lay Ergün, & Erbaş, 2002; Brokate et al., 2003; Uekermann, Daum, Schlebusch, Wiebel, & Trenckmann, 2003; Fama, Pfefferbaum, & Sullivan, 2004). The lateralization hypothesis assumes that functions associated with the right hemisphere are most affected by alcohol abuse (Ratti, Bo, Giardini, & Soragna, 2002). The third hypothesis of diffuse brain dysfunction assumes that cognitive deficits resulting from alcohol abuse are diffuse and not tied to a specific region of the brain (Ratti et al., 1999). The current body of literature supports the diffuse brain dysfunction hypothesis when determining the extent and location of the effects of prolonged alcohol abuse on the brain. Attention, working memory, speed of processing,

visuospatial abilities, executive functions, impulsivity, learning, memory, and verbal fluency have all been shown to be impaired in alcoholism (Stavro, Pelletier, & Potvin, 2013; Oscar-Berman & Marinkovic, 2007). There is some argument that alcohol abuse shows only negligible consequences on cognitive functioning if use is short-lived (Eckardt et al., 1998). Eckardt et al., (1998) proposed that only after 10 years of alcohol abuse do neuropsychological deficits become apparent. Alternatively, cognitive deficits have also been shown to be stable even during and up to the one-year milestone of sobriety (Stavro, Pelletier, & Potvin, 2013). Cognitive recovery has also been found to be possible with prolonged abstinence (Parsons, 1998; Rourke & Grant, 1999; Stavro, Pelletier, & Potvin, 2013).

General intelligence. One study measured IQ scores and accounted for both total alcohol consumption and binge drinking (Sjölund et al., 2015). They found a significant correlation between IQ scores and total alcohol intake with lower IQ scores being associated with higher alcohol consumption (Sjölund et al., 2015). Similar results were found in an earlier study when accounting for frequency of alcohol use (Muller et al., 2013). Additionally, in terms of overall functioning, nonverbal tasks appear to be compromised more significantly than verbal tasks which provides support for the lateralization hypothesis (Parsons & Leber, 1981).

Executive functioning and language. Executive functioning abilities have been observed to decline following alcohol abuse (Scheurich, 2005). After 6 months of abstinence by chronic alcohol abusers, executive functioning has been shown to improve to normal levels (Pitel et al., 2009). Age was shown to be a mediating factor for executive recovery with younger recently abstained abusers having better recovery of executive functioning (Pitel et al., 2009). Less plasticity of an older adult brain is a contributing factor to less recovery of executive functioning in older adults following abstinence (Fein, Bachman, Fisher, & Davenport, 1990;

Munro, Saxton, & Butters, 2000; Rourke & Grant, 1999). Current literature suggests that moderate alcohol use does not have long-term consequences on confrontation naming tasks or semantic fluency, but verbal fluency was shown to decline significantly faster in individuals with heavier alcohol use (Topiwala et al., 2017).

Attention and working memory. Attention and working memory deficits are commonly seen in individuals with a history of alcohol abuse (Scheurich, 2005). Following 5-6 weeks of abstinence, a return to normal levels of N-acetylasparate in the cerebellum is significantly correlated with improved attention span in chronic alcohol abusers (Bendszus et al., 2001). Other literature is suggestive of more prolonged deficits in attention, even following a period of abstinence (De Sousa Uva et al., 2010; Fortier et al., 2014; Weiland et al., 2014).

Processing speed. Motor speed was found to be significantly slower in individuals with alcohol use disorder (Sher, Martin, Wood, & Rutledge, 1997). Similar results were found in patients with alcohol use who experienced impairment in tasks involving perceptual motor speed (Tivis, Beatty, Nixon, & Parsons, 1995). With increased age, alcohol using individuals were found to perform significantly slower on tasks requiring psychomotor processing than their non-drinking counterparts (Bourke & Grant, 1999).

Memory. Fractional anisotropy values of white matter structures within the reward system have negative correlations with memory function in individuals with prolonged alcohol abuse (Trivedi et al., 2013). Memory was significantly negatively correlated with lifetime alcohol consumptions, meaning the more alcohol that was consumed throughout the life, the lower memory scores were (Eckardt, Stapleton, Rawlings, Davis, & Grodin, 1995). Alcohol lowers NMDA activity while present which impairs learning and memory (Zeigler et al., 2005). Both verbal and nonverbal recall are impacted by alcohol abuse (Brown, Tapert, Grahholm, &

Delis, 2000). In chronic alcohol abusers who have been abstinent for 5-6 weeks, a return to normal levels of N-acetylasparate in the frontal lobe is significantly correlated with improved verbal and learning memory (Bendszus et al., 2001). Verbal memory was also found to improve to normal levels following a 6-month abstinence period in chronic alcohol users (Pitel et al., 2009). Alcohol abuse duration was a mediating factor in verbal memory recovery with shorter abuse duration leading to a greater likelihood of episodic memory recovery (Pitel et al., 2009).

Visuospatial. Deficits in visuospatial abilities are commonly seen following alcohol abuse (Bowden & McCarter, 1993; Ellis & Oscar-Burman, 1989; Parsons, 1987; Scheurich, 2005). Perceptual-motor deficits have also been noted following prolonged alcohol abuse (Bowden & McCarter, 1993; Ellis & Oscar-Burman, 1989; Parsons, 1987). Individuals who consume at least moderate amounts of alcohol shower poorer performance than healthy control in tasks requiring visuospatial abilities (Green et al., 2010). Tasks requiring visuospatial abilities were also found to be impaired in a group of individuals who have recently detoxified from alcohol (Dawson & Grant, 2000).

Emotional, affect, and personality. The diminishing ability for chronic alcohol users to recognize affective expressions in human faces has been well documented (Clark, Oscar-Berman, Shagrin, & Pencina, 2007; Foisy et al., 2005; Kornreich et al., 2002; Phillippot et al., 1999; Townshend & Duka, 2003). The ability to distinguish affective cues has also been shown to decrease in chronic alcohol abusers (Monnot, Lovallo, Nixon, & Ross, 2002). Undifferentiated affective response to emotional stimuli is common in chronic alcohol abusers which lends itself to interpersonal difficulties (Kornreich et al., 2002). Depression is a common finding in chronic alcohol abusers (Zeigler et al., 2005). Two common hypotheses exist as to the correlation between depression and alcohol abuse. The first is the self-medication hypothesis that posits

individuals drink alcohol because they are depressed (Zeigler et al., 2005). The other hypothesizes that depression is a result of alcohol's contribution to the significant reduction of neurons in the locus coeruleus which changes norandrenergic neurotransmission (Zeigler et al., 2005).

Imaging.

Computed tomography. Findings are inconsistent in terms of lateralization of structural damage following chronic alcohol abuse. No size differences were found between the hemispheres in a post mortem study (Harper, Krill, & Holloway, 1985). Some CT studies have shown no differences between the hemispheres (Lee, Moller, Hardt, Haubek, & Jensen, 1985; Wilkinson & Carlen, 1979) while others describe more pronounced changes in the left hemisphere than the right (Gebhardt, Naeser, & Butters, 1984; Golden et al., 1981). CT scans have also shown wider sulci in the cerebrum and enlarged ventricles suggestive of atrophy (Pfefferbaum, Rosenbloom, Crusan, & Jernigan, 1988).

Magnetic resonance spectroscopy. There has been a recent increased interest in the use of magnetic resonance spectroscopy in psychiatric disorders including alcohol use (Bendszus et al., 2001; Nery et al., 2010; Thoma et al., 2011). Magnetic resonance spectroscopy provides a noninvasive way to quantify metabolites in a specific region of the brain to study metabolic change (Hermens et al., 2013). Specifically, studies on alcohol use the proton 1H-MRS to determine the viability of neurons through N-acetylasparate as well as glutamate (Hermens et al., 2013). Pre-atrophic white matter n-acetylasparate reductions have been found is heavy alcohol users (Fein et al., 2002).

Magnetic resonance imaging. MRI studies reveal volume loss in the frontal lobes of chronic alcohol abusers (Pfefferbaum, Sullivan, Mathalon, & Lim, 1997). MRI studies have also

revealed volumetric deficits in the extended reward and oversight center in the brain's right hemisphere (Makris et al., 2007). The extended reward and oversight center includes dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortices, the anterior insula, hippocampus, amygdala, nucleus accumbens, and ventral diencephalon. (Oscar-Berman & Marinkovic, 2014). A reduction of hippocampal volume has been found in chronic alcohol abusers using structural imaging techniques (Agartz, Momenan, Rawling, Kerich, & Hommer, 1999; Beresford et al., 2006; Kurth et al., 2004; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995). Some studies show more significant right hippocampal atrophy in chronic alcohol abusers (Laakso et al., 2000) while other studies show greater volume loss of the left hippocampus (Beresford et al., 2006). The decrease in hippocampal volume can be reversed following a short period of abstinence (White, Mathews, & Best, 2000).

Functional magnetic resonance imaging. Functional magnetic resonance imaging (fMRI) has provided additional evidence of reduced activation in the amygdala and hippocampus of chronic alcohol abusers when presented with emotional words and expressions (Marinkovic et al., 2007). fMRI findings show that even on a verbal task in which alcohol abusers perform similarly to control groups, the alcohol abusers have significantly more activation in the right superior cerebellar and left frontal regions (Desmond et al., 2003) which may indicate increased demand on the frontal regions to overcome impairments related to chronic alcohol abuse (Sullivan et al., 2003). fMRI also revealed structural abnormalities in the frontal lobes of chronic alcohol abusers (Tapert et al., 2001). During a task of spatial working memory, alcohol-dependent females showed less functional activity in the frontal and parietal lobes in the right hemisphere when compared to healthy controls (Sher, Martin, Wood, & Rutledge, 1997).

Older Adults

Functional and structural changes can be very diverse in the aging process. Changes can occur in a multitude of different domains and can have a wide range of outcomes. Addressed in the current section are physiological and neuropsychological changes in older adults experiencing healthy aging without the presence of severe pathology.

Apolipoprotein E

Apolipoprotein E (ApoE) is a lipoprotein which serves to transport cholesterol from the blood (Taylor et al., 2017). Located on chromosome 19, ApoE genetic coding has three variations of alleles, E2, E3, and E4 (Taylor et al., 2017). It is largely believed that having the ApoE E4 allele is the most predictive risk factor for Alzheimer's disease (Corder et al., 1993). Cognitive differences have been observed in carriers of the ApoE E4 allele even in healthy older adults when compared to individuals who do not have the E4 variant (Caselli et al., 2004). On the other hand, individuals with the ApoE E2 allele variant have been shown to have less cognitive decline than their E4 carrying counterparts and the ApoE E2 allele variant may have protective factors against Alzheimer's disease (Suri et al., 2013).

Cellular Changes.

Gray matter changes. Cortical structures show a loss in volume in the healthy aging brain (Raz et al., 2005). The frontal lobe hypothesis of aging (West, 2000) shows the most pronounced volume loss during the normal aging process is centered around the frontal cortices, with less profound volume loss in the parietal and temporal lobes (Smith et al., 2007; Terribilli et al., 2011). The use of alcohol may accelerate neuronal loss in older adults with the frontal lobes being most affected (Harper et al., 1998). Synapsis also become less dense during the aging process due to synaptic pruning and reduced synapse plasticity (Masliah, Crews, & Hansen,

2006). While some neuronal loss and volume reduction can be expected during the normal aging process, it is believed that individuals with the ApoE E4 allele variant will show smaller cortical and subcortical volume as well as increased rates of atrophy when compared to individuals without the allele variant (Donix et al., 2010, Risacher et al., 2010).

White matter changes. White matter changes are commonly seen following changes in gray matter (Salat, Kaye, & Janowsky, 1999). White matter changes often occur around age 70 (Salat, Kaye, & Janowsky, 1999) with an individual losing almost half of their white matter volume between age 20 and age 80 (Marner, Nyengaard, Tang, & Pakkenberg, 2003). Volume loss in the anterior cortex has been found in aging individuals and can also affect the structural integrity of frontal lobe white matter (O'Sullivan, Jones, Summers, Morris, Williams, & Markus, 2001; Pfefferbaum, Adalsteinsson, & Sullivan, 2005). Metabolism and blood flow have also been found to be decreased in the frontal region (Tumeh et al., 2007), however, it is unclear whether the decreased metabolism and blood flow in the frontal lobe cause its vulnerability to aging or if it a result of the vulnerability itself (Greenwood, 2000).

Neuropsychological changes.

A large portion of current literature uses comparisons between healthy older adults and cohorts of younger individuals. Compared to younger individuals, healthy older adults appear to show impairment in processing speed, working memory, and executive functioning (Dennis & Cabeza, 2008). Different theories exist as to the profile of a healthy aging individual. Some argue that deficits due to a reduction of processing speed are the causes of cognitive and perceptual changes which highlight functional decline (Madden, 2001; Salthouse, 1996). Others suggest that a decline in executive functioning and inhibition are the hallmarks of decline due to healthy aging (Dempster, 1992; Hasher & Zacks, 1988).

When gaining perspective on the neuropsychological functioning of older adults, it is essential to consider other factors that may influence testing performance. Although some decline in neuropsychological performance can be expected even in healthy aging older adults, factors such as years of education and intelligence might have a protective quality on cognitive functioning (Stern, 2009). The theory of cognitive reserve posits that education and intelligence can have beneficial effects on the functioning and structure of the brain because the differences in neural networks allow for better coping and compensation of affected areas of the brain (Stern, 2006, Stern, 2009). Conversely, cognition decline can also be exacerbated by diseases such as diabetes and hypertension amongst others (Moretti et al., 2012).

Processing speed. Anterior cortical functioning has been shown to decrease in the healthy aging brain (West, 1996). The anterior cortex is responsible for tasks such as processing speed and information selection (Madden, 2001; Salthouse, 1996). In the theory proposed by Salthouse (1996) suggesting that processing speed is the major declining function of healthy older adults, he posited that fluid intelligence decline could be attributed to the deficit found in processing speed. In an early study, Salthouse (1992) found a significant difference on the Wechsler Adult Intelligence Scale Digit Symbol Substitution Test in which completion times were slower for older adults. Significantly slower processing speed was also noted on the identical pictures and finding A's test (Schaie, 1989) and pattern comparison test (Salthouse, 1993). Factors such as health, task familiarity, and factors specific to each test can mediate the amount of deficit shown on a given task (Salthouse, 2000).

Working Memory. Working memory deficits in older adults is a product of the central executive system which, according to a model proposed by Baddeley (2000), is comprised of three systems coordinated by the central executive system. The phonological loop of the central

executive system, located in the left ventrolateral prefrontal cortex (Paulesu, Frith, & Frackowiak, 1993), is responsible for language information (Baddeley, 2000). The visuospatial sketchpad of the central executive system is responsible for visuospatial information (Baddeley, 2000). The episodic buffer of the central executive system is used to integrate information (Baddeley, 2000). A prominent argument for the role of the central executive system (Reuter-Lorenz & Sylvester, 2004) is grounded in evidence that older adults and younger controls perform similar in word span and digit span abilities but show remarkable differences when mental manipulation of stored information is required (Dobbs & Rule, 1989; Fisk & Warr, 1996; Gick, Craik & Morris, 1988). Imaging consistently shows the dorsolateral prefrontal cortex as a key location for working memory functions of manipulating verbal and spatial information (Barbey et al., 2013; Petrides, 2000). Additionally, individuals with lesions to the dorsolateral prefrontal cortex do not experience deficits in information storage (Henson, 2001).

Executive functioning. In contrast to normal declines in executive functioning due to aging, individuals with Alzheimer's disease also exhibit additional declines in functioning such as declarative memory (Huppert, 1994) and visual deficits (Renner, Burns, Hou, McKeel, Storandt, & Morris, 2004). The ability for appropriate inhibition is found to decline in the normal aging process (Hasher, Stoltzfus, Zacks, & Rypma, 1991; McDowd, 1997) and has largely been attributed to volume loss in the inferior frontal gyrus (Aron et al., 2004). Attentional deficits have also been found in older adults when compared to their younger counterparts (Watson & Maylor, 2002).

Language. Language decline in older adults has been found to generally occur after age 70 (Kent & Luszcz, 2002). Other literature has found no decline in tasks specific to naming (Heaton et al., 1999; Tombaugh & Hubley, 1997). A phenomenon known as tip-of-the-tongue is

also more prevalent with older adults. Tip-of-the-tongue occurs when an individual knows the word they want to say and can explain the word, but they are not able to say the exact word (Cross & Burke, 2004).

Traumatic Brain Injury and Alcohol Abuse

Animal studies have demonstrated the effects that a traumatic brain injury has on the blood-brain-barrier when alcohol is introduced. Interestingly, the time of alcohol intake in relation to brain injury was the crucial component (Persson & Rosengren, 1977). Blood-brain-barrier permeability was increased only in animals who were intoxicated at the time of injury, but if alcohol was administered 24 hours prior to an injury, the effects were largely mitigated (Persson & Rosengren, 1977). Traumatic brain injuries occurring in individuals with a history of chronic alcohol abuse can lead to complicating secondary injuries of the CNS due to hepatic encephalopathy, central pontine myelinolysis, or nutritional deficiencies pellagrous encephalopathy due to niacin deficiency (Charness, 1993).

Reports suggest that alcohol is a significant factor in repeat trauma admissions with 44% due to alcohol problems (Rivara et al., 1993) and up to 28% of all trauma admissions meeting criteria for alcohol dependence (Soderstrom et al., 1997). There is a large body of literature focusing on the effects of day-of-injury alcohol use on neurocognitive recovery, however, the findings are inconsistent. The majority of research supports the notion that deficits in global cognitive and neurobehavioral status (Sparadeo & Gill, 1989), verbal ability, visuospatial ability, executive functioning, processing speed, immediate memory, and delayed memory (Bombardier & Thurber, 1998; Kelly, Johnson, Knoller, & Drubach, 1997; Tate, Freed, Bombardier, Harter, & Brinkman, 1999; Wilde et al., 2004) are more prevalent in individuals who have consumed alcohol on the day of the TBI than individuals who did not consume alcohol. Others have found

that chronic alcohol abuse prior to TBI is a more significant factor in neuropsychological decline than day-of-injury intoxication (Lange, Iverson, & Franzen, 2007) while others have found that chronic alcohol abuse and day-of-injury alcohol abuse are equal contributors (Wilde et al., 2004) and still others have found negligible effects between the two (Vickery et al., 2008). Full-scale IQ and verbal IQ are significantly lower in individuals with positive alcohol screen following severe TBI when compared to control groups (Kelly, Johnson, Knoller, Drubach, & Winslow, 2009).

Changes in alcohol consumption following TBI are not uncommon. Some individuals with drinking problems prior to TBI may discontinue use following the injury (Hibbard, Uysal, Kepler, Bogdany, & Silver, 1998). Conversely, approximately 20% of individuals who reported heavy drinking following TBI described only light alcohol consumption or no alcohol consumption prior to TBI (Corrigan, Lamb-Hart, & Rust, 1995). And still another group who showed problematic alcohol use prior to TBI declined in self-reported alcohol problems following TBI (Kreutzer, Doherty, Harris, & Zasler, 1990). Additionally, one study found that individuals with significant self-reported alcohol problems prior to injury were ten times more likely to report significant alcohol-related problems following injury than individuals who reported abstinence or normal drinking prior to injury (Bombardier, Temkin, Machamer, & Dikmen, 2003).

Traumatic Brain Injury and Older Adults

There is a large body of literature regarding TBI and the onset of dementia. Most of the research has determined that individuals with a history of traumatic brain injury earlier in life were at higher risk for developing dementia as an older adult (Ashman et al., 2008; Bazarian, Cernak, Noble-Haeusslein, Potolicchia, & Temkin, 2009; French et al., 1985). In older adults, it

is apparent that the severity of an injury is the best predictor of outcome following a traumatic brain injury (Dikmen, Machamer, Savoie, & Temkin, 1996). Goldstein, Levin, Goldman, Clark, and Altonen (2001) found that older adults who have experienced a moderate TBI experienced earlier cognitive deficits of attention, memory, expressive language, and executive functioning when compared to those individuals who experienced a mild TBI. Severe TBI can be accompanied by significant mortality as well as longer lasting disabilities (Mosenthal et al., 2004). A history of substance abuse has also been shown to be a contributing factor to poorer outcomes following TBI (Martin & Johnstone, 2005). Genetic factors such as the presence of the ApoE E4 allele variant contribute to worse short-and long-term recovery following TBI (Crawford et al., 2002; Hartman et al., 2002). Consistent with the cognitive reserve theory, larger brain volume and higher levels of education have been associated with more positive outcomes in older adults following TBI (Kesler, Adams, Blasey, & Bigler, 2003).

CHAPTER III: METHODOLOGY

Data Use

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI database was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

Participants

As of December 19, 2018, the database included 271 subjects. Of the participants, 268 (98.9%) were male and 2 (0.7%) were female with 1 (0.4%) participant not disclosing gender. The majority of participants were between the ages of 60-69 (n = 169, 62.4%) and an additional 31.7% (n = 86) were between the ages of 70-79. Ten (3.7%) were between the ages of 80-89 and an additional 2.2% (n = 6) did not have age data available. All participants provided informed consent to allow their results and clinical information to be collected and used as part of the DOD-ADNI study in accordance with the San Francisco Veteran Affairs Medical Center Institutional Review Board standards and regulations.

Participants were separated into three categories for the purpose of sample breakdown in the DOD-ADNI study: (1) Vietnam Veterans with TBI, but without PTSD, MCI, or dementia, (2) Vietnam Veterans with PTSD, but without TBI, MCI, or dementia, and (3) Vietnam Veteran controls, without TBI to PTSD and comparable in age, gender, and education to other groups.

Individuals with MCI or dementia were excluded from the study because of the difficulty differentiating between the effects of PTSD/TBI from Alzheimer's disease pathology (DOD-ADNI Approved final protocol, 2012).

Inclusion and Exclusion Criteria.

DOD-ADNI traumatic brain injury inclusion criteria. According to the DOD-ADNI protocol, individuals being considered for placement in the traumatic brain injury group must meet eligibility criteria. Each individual must be a veteran of the Vietnam War. They must be between 50 and 90 years of age at the time of enrollment. Each individual must have a moderate to severe non-penetrating TBI which occurred during military service in Vietnam, as confirmed by the Department of Defense or Veteran's Administration records. Additionally, all eligible individuals must live within 150 miles of the closest ADNI clinic in the subject's area. Moderate to severe TBI is identified in the study by (1) loss of consciousness, (2) post-traumatic amnesia greater than 24 hours, or (3) alterations of consciousness or mental state greater than 24 hours.

DOD-ADNI traumatic brain injury exclusion criteria. DOD-ADNI protocol manual outlines criteria in which individuals are considered not eligible for the study. If an individual is found to have mild cognitive impairment or dementia, they are no longer eligible for the study. Additionally, if a diagnosis of posttraumatic stress disorder (PTSD) is determined by either the SCID-IV or the Clinician-Administered PTSD Scale (CAPS) score greater than 30, the individual is no longer considered eligible to be included in the database. Both current and/or prior history of PTSD were excluded from the DOD-ADNI database.

DOD-ADNI control group inclusion criteria. DOD-ADNI protocol manual set forth criteria that must be met to qualify for the control group of the study. Each individual must be a veteran of the Vietnam War. They must have been between the ages of 50 and 90 at the time of

enrollment. The group needed to be comparable in terms of age, gender and, education with the traumatic brain injury group. The individual may be receiving disability from Veterans Affairs, but the payments must not be related to TBI or PTSD. Each individual must live within 150 miles of the closest ADNI clinic in the subject's area.

DOD-ADNI control group exclusion criteria. DOD-ADNI protocol manual detailed criteria which excluded individuals from being considered for the control group. Individuals must not have been diagnosed with mild cognitive impairment or dementia. Additionally, if a diagnosis of PTSD is determined by either the SCID-IV or a CAPS score greater than 30, the individual is no longer considered eligible to be included in the database. Past and current PTSD is excluded. If the individual has a documented or self-reported history of TBI, they would no longer be eligible for the control group. Furthermore, if an individual has experienced a head trauma which resulted in cognitive complaints, they would be excluded from the control group. Also, if the individual has experienced a loss of consciousness greater than 5 minutes, they are not eligible for the control group.

DOD-ADNI exclusion criteria for all subjects. DOD-ADNI protocol manual outlined criteria which made subjects ineligible to participate in their study. If an individual had been diagnosed with mild cognitive impairment or dementia, they were not considered for the study. Also, if an individual had a history of psychosis or bipolar affective disorder, they were found to be ineligible. History of alcohol abuse or dependence within five years of study participation rendered the individual ineligible. Magnetic resonance imaging (MRI) factors that made an individual ineligible included aneurysm clips, metal implants that are determined to be unsafe for MRI, and/or claustrophobia. Any individuals who were not appropriate for lumbar puncture, positron emission tomography scan, or other procedures in the study were excluded. If an

individual has experienced any major medical condition, the condition must have been stable for at least four months before the individual was considered for the study. Examples of major medical conditions identified by DOD-ADNI included but were not limited to clinically significant hepatic, renal, pulmonary, metabolic or endocrine disease, cancer, HIV infection and AIDS, as well as cardiovascular disease. Cardiovascular diseases considered were cardiac surgery or myocardial infarction within four weeks prior to consideration, unstable angina, acute decompensated congestive heart failure or class IV heart failures, current significant cardiac arrhythmia or conduction disturbances particularly those resulting in ventricular fibrillation or causing syncope, and high blood pressure. Additionally, individuals with any seizure disorder or other systemic illness affecting brain functioning during the five years prior to study enrollment were excluded, as were individuals with clinical evidence of stroke. Individuals with a relevant history of severe drug reactions or hypersensitivity to medications were not considered for the DOD-ADNI study. Finally, individuals with unstable medical comorbidities found upon record review or physical examination were excluded if it was determined that the comorbidity posed a safety risk to the individual.

Current study participants. The current study consists of a three-group comparison of individuals (1) with a history of moderate to severe traumatic brain injury and a history of alcohol abuse or dependence (ALC group), (2) with a history of moderate to severe traumatic brain injury and no history of alcohol abuse or dependence (No-ALC group), and (3) with no history of moderate to severe traumatic brain injury and no history of alcohol abuse or dependence (control group). History of traumatic brain injury was confirmed by record review and SCID-IV interview by staff at the San Francisco VAMC. History of alcohol use was determined by SCID-IV interview by staff at the San Francisco VAMC. In addition to the

inclusion and exclusion criteria set forth by DOD-ADNI, the current study included additional criteria. Both current and/or prior history of PTSD were excluded from the current database. Additionally, only individuals who participated in the screening and baseline assessments were included. All individuals who were included in the database took part in the SCID-IV interview.

Neuropsychological Measures

DOD-ADNI neuropsychological measures. DOD-ADNI protocol used multiple time periods for testing individuals. During the initial visit to the screening site, participants were administered the Mini Mental Status Examination (Folstein & Folstein, 2001) and the Wechsler Memory Scale-Revised (WMS-R) Logical Memory I and II (Wechsler, 1987). Upon returning to the DOD-ADNI site for a baseline visit, the participant was administered a full battery of neuropsychological measures. A standardized order of administration was encouraged by the DOD-ADNI protocol manual to ensure inter-rater reliability. The following order was used to administer assessments during the baseline site visit:

1. American National Adult Reading Test (Grober & Sliwinski, 1991)
2. Alzheimer's Disease Assessment Scale-Cognitive (Rosen, Mohs, & Davis, 1984)
3. Everyday Cognition- Participant Self-Report (Farias et al., 2008)
4. Everyday Cognition- Study Partner Report (Farias et al., 2008)
5. Rey Auditory Verbal Learning Test (Trials 1-6; Rey, 1964)
6. Montreal Cognitive Assessment (Nasreddine et al., 2005)
7. Clock Drawing (Kaplan & Goodglass, 1983)
8. Category Fluency (animals; Morris et al., 1989)
9. Trails A and B (Reitan, 1992; Reitan & Wolfson, 1993)
10. Boston Naming Test (30-item; Kaplan, Goodglass, & Weintraub, 1983)

11. Rey Auditory Verbal Learning Test (30-minute Delay; Rey, 1964)

12. Armed Forces Qualification Test (Bayroff & Anderson, 1963)

In addition to cognitive measures, DOD-ADNI used a variety of other measures to assess psychiatric symptoms. The Geriatric Depression Scale (Sheikh & Yesavage, 1986) was used to assess symptoms commonly associated with depression in older adults. The Neuropsychiatric Inventory (Cummings, 1994) was used to assess behaviors commonly related to dementia. The Clinical Dementia Rating Scale (Morris, 1993) was used to determine the presence of cognitive impairment.

Current study neuropsychological measures. The current study used select measures that were administered during the initial visit to the screening site and others that were administered during the baseline visit to the screening site.

Executive functioning. Part B of the Trail Making Test (Reitan, 1992; Reitan & Wolfson, 1993) and The Controlled Oral Word Association Test (COWAT), Semantic Fluency (Benton & Hamsher, 1983; Benton, Sivan, Hamsher, Varney, & Spreen, 1994) were used to determine executive functioning of the participants in the current study. Part B of the Trail Making Test (Reitan, 1992; Reitan & Wolfson, 1993) requires that the participant connect 25 randomly placed encircled numbers and letters in a sequential manner alternating between number and letter (Strauss, Sherman, & Spreen, 2006). The total time for completion is recorded (Strauss, Sherman, & Spreen, 2006). The participants are given a practice trial to ensure understanding of the task (Strauss, Sherman, & Spreen, 2006). The COWAT semantic fluency task requires the participant to produce as many words as possible from a specific category provided by the examiner (Strauss, Sherman, & Spreen, 2006). The most common category used for semantic fluency is “animals” (Strauss, Sherman, & Spreen, 2006). The participant is given

one minute to produce as many words as possible from the given category (Strauss, Sherman, & Spreen, 2006). The total number of unique words produced during the trial is recorded (Strauss, Sherman, & Spreen, 2006).

Verbal memory. The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) requires that the participant produce words after being read a list of 15 words by the examiner (Rey, 1964). The participant is given five trials in which the list of words is read to them each time, and they must produce as many words as they can from memory (Rey, 1964). A second list of words is then read by the examiner, and the participant must produce words only from the second list (Rey, 1964). Following the second list of words, the participant must produce words from the original list spontaneously (Rey, 1964). Following a 30-minute delay, the participant must again spontaneously produce words from the original list (Rey, 1964). A recognition trial is given in which the participant must circle the words that were on the first list when given a list of words. Total scores for trials 1-6, delayed recall, and intrusions are recorded for the DOD-ADNI protocol (2017). Logical memory from the Wechsler Memory Scale-Revised (WMS-R; Wechsler 1987) requires individuals to recall a story after being read the story by an examiner. Logical Memory I requires an individual to repeat one story immediately after hearing it, which is given to them verbally by the examiner (Wechsler, 1987). The story is awarded a maximum of 25 points for correct recall of details. The raw score of Logical Memory I is the total number of items correctly recalled. Logical Memory II requires an individual to recall as many details from the story as possible following a break of 30 to 40 minutes (Wechsler, 1987). The break is filled with tasks which do not require verbal memory. The story recall score is awarded a maximum of 25 points. The raw score for Logical Memory II is the total details correctly recalled from the story.

Confrontation naming. The 30-item Boston Naming Test requires an individual to correctly name the item of a picture presented to them (Kaplan, Goodglass, & Weintraub, 1983). For the purpose of \ DOD-ADNI \ (2017), only the odd numbers of the 60-item Boston Naming Test were administered. Each stimulus is a drawing of objects ranging from commonly seen objects to rarely seen objects. An individual is required to produce a spontaneous answer within 20 seconds of the stimulus being presented. If the individual provides a correct response spontaneously, a check is placed in the "uncued response" column of the scoresheet. If the individual clearly misperceives the drawing, a stimulus cue is presented. If a correct response is supplied following a semantic cue, a check is placed on the scoresheet under the "correct with semantic cue" column. If after 20 seconds the individual does not produce a correct response, a phonemic cue is given. If the individual correctly names the drawing after the phonemic cue, a check is placed on the scoresheet in the "correct with a phonemic cue" column. If the individual fails to produce a correct response following the phonemic cue, a check is placed in the "incorrect with phonemic cue" column of the scoresheet. The test is discontinued upon completion of all items or if the individual provides incorrect responses to six consecutive items. Six total scores are given: (1) total correct without a cue, (2) total semantic cues given, (3) total correct with a semantic cue, (4) total phonemic cues given, (5) total correct with phonemic cues, and (6) total correct without a cue plus total correct with a semantic cue.

Processing speed. Part A of the Trail Making Test requires the participant to connect 25 randomly placed encircled numbers sequentially as fast as possible without making mistakes (Strauss, Sherman, & Spreen, 2006). The participant's total time is recorded (Strauss, Sherman, & Spreen, 2006). To ensure an understanding of the task, the participant is first provided with a

shorter practice trial which does not contribute to their total score (Strauss, Sherman, & Spreen, 2006).

Psychological functioning. The Geriatric Depression Scale is a 15-item screening questionnaire administered by the site staff (Sheikh & Yesavage, 1986). The participant is instructed to answer with a "yes" or "no" to the questions which ask about various aspects of feelings in the week prior to the interview. Answers written in bold on the answer sheet are scored with a "1". According to the DOD-ADNI (2017) protocol, scores >5 are suggestive of depression, whereas scores >10 are almost always indicative of depression.

Alcohol Use Measures

DSM-IV-TR. Substance Dependence. The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (American Psychiatric Association, 2000) set forth the following criteria which were used to determine substance dependence in participants:

1. A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in a 12-month period:
    a. Tolerance, as defined by either of the following:
        i. a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or
        ii. markedly diminished effect with continued use of the same amount of the substance
    b. Withdrawal, as manifested by either of the following:
        i. the characteristic withdrawal syndrome for the substance, or

ii. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms

c. The substance is often taken in larger amounts or over a longer period than intended

d. There is a persistent desire or unsuccessful efforts to cut down or control substance use

e. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects

f. Important social, occupational, or recreational activities are given up or reduced because of substance use

g. The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

DSM-IV-TR. Substance abuse. A substance abuse diagnosis was considered when the following DSM-IV-TR criteria were met:

1. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

    a. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance

related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

b. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating machinery when impaired by substance use)

c. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)

d. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights).

Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Version IV. The *Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Version IV* (SCID-IV; First, Spitzer, Gibbon, & Williams, 1996) is a semi-structured clinical interview used to standardize information gathering procedures (First, Spitzer, Gibbon, & Williams, 1996). It includes questions and decision-making processes for DSM-IV Axis I disorders. The SCID-IV Module E: Substance Use Disorders asks questions specific to the individual's lifetime drug and alcohol usage. Module E inquires about an individual's drinking habits throughout their lifetime, including frequency, amount, and duration. Module E is separated into alcohol abuse and alcohol dependence according to the unique diagnostic criteria for each. Module E was used to separate participants into groups based on alcohol use.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp., 2018) was used for all statistical analyses. Descriptive statistics and frequencies were used to determine demographic variables. Statistical differences between groups within categorical variables were assessed using a chi-square test for independence. Statistical differences between groups on continuous demographic variables were assessed using a one-way between groups analysis of variance (ANOVA). Preliminary analyses were conducted to ensure no violation of assumptions on neuropsychological variables. It was also determined that five neuropsychological measures were not normally distributed. The Boston Naming Test, WMS-R Logical Memory I, Trailmaking Test A, Trailmaking Test B, and Geriatric Depression Scale were not normally distributed. To account for the known effects of age, education level, and APOE4 allele, these factors were used as covariates. Differences between groups on normally distributed variables were analyzed using analyses of covariance (ANCOVA). Differences between groups on non-normally distributed variables were analyzed using the Kruskal-Wallis Test. Significance level of $p < 0.05$ was used to determine statistical significance.

CHAPTER IV: RESULTS

On average, the participants (N = 83) were 71 years of age (M = 70.9, SD = 5.9) and ranged from 61 to 85. All included participants were male who spoke English as a first language. Females and individuals not reporting a gender were not included in the study. The participants had approximately 16 years of formal education (M = 16.2, SD = 2.2) and ranged from 12 years to 20 years of formal education. Most (86.7%) of the sample was Caucasian. A large majority of participants were right-handed (90.4%). 73 (88.0%) participants reported being married, and an additional 7 (8.4%) were divorced. Approximately three-fourths (74.7%) were retired. Complete participant demographics can are shown in Table 1.

Table 1.

Demographic data

Variable	Full Sample (N=83)	TBI-Alcohol (n=10)	TBI-No Alcohol (n=29)	Control (n=44)	F/X^2	p
Age	70.9 (5.9)	70.1 (4.6)	70.4 (6.1)	71.5 (6.1)	0.373	0.690
Handedness					3.393	0.183
Right	75 (90.4%)	10 (100.0%)	24 (82.8%)	41 (93.2%)		
Left	8 (9.6%)	0 (0.0%)	5 (17.2%)	3 (6.8%)		
Marital status					11.620	0.071
Married	73 (88.0%)	6 (60%)	28 (96.6%)	39 (88.6%)		
Widowed	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		
Divorced	7 (8.4%)	3 (30.0%)	1 (3.4%)	3 (6.8%)		
Never Married	2 (2.4%)	1 (10.0%)	0 (0.0%)	1 (2.3%)		
Education (years)	16.2 (2.2)	15.7 (3.0)	16.4 (2.0)	16.1 (2.1)	0.429	0.653
Retirement status					3.595	0.166
Not Retired	21 (25.3%)	4 (40.0%)	4 (13.8%)	13 (29.5%)		
Retired	62 (74.7%)	6 (60.0%)	25 (86.2%)	31 (70.5%)		
Racial category					11.400	0.327
American Indian or Alaskan Native	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		
Asian	2 (2.4%	0 (0.0%)	0 (0.0%)	2 (4.5%)		
Black or African American	4 (4.8%)	2 (20.0%)	0 (0.0%)	2 (4.5%)		
White	72 (86.7%)	8 (80.0%)	27 (93.1%)	37 (84.1%)		
More than one race	3 (3.6%)	0 (0.0%)	2 (6.9%)	1 (2.3%)		
Unknown	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		
ApoE E4 Allele present					3.015	0.221
No	56 (67.5%)	4 (40.0%)	18 (62.1%)	34 (77.3%)		
Yes	19 (22.9%)	4 (40.0%)	6 (20.7%)	9 (20.5%)		
Unknown	8 (9.6%)	2 (20.0%)	5 (17.2%)	1 (2.3%)		

Note: Means (SD) or frequencies (%) are reported for each variable; SD=Standard Deviation; X^2=Chi squared test for independence; p=significance level; *$p < 0.05$.

Participants who experienced a moderate-severe traumatic brain injury and a history of alcohol abuse or dependence were allocated to the TBI-Alcohol group. Participants in the TBI-Alcohol group (n = 10) were approximately 70 years old (M = 70.1, SD = 4.6) with an average of 15.7 (SD = 3.0) years of education. All participants in the group were right-handed. Sixty percent were married with an additional 30.0% divorced. Sixty percent were retired. Eighty

percent of the participants in the group were Caucasian, and 20% were Black or African American.

Participants who experienced a moderate-severe traumatic brain injury and did not have a history of alcohol abuse or dependence were allocated to the TBI-No Alcohol group. Participants in the TBI- No Alcohol group (n = 29) were approximately 70 years old (M = 70.4, SD = 6.1) with an average of 16.4 (SD = 2.0) years of education. A majority of the participants in the group were right-handed (82.8%). Twenty-eight (96.6%) were married. A majority (86.2%) were retired. Most (93.1%) of the participants in the group were Caucasian, and two more (6.9%) were more than one race.

Participants who have not experienced a moderate-severe traumatic brain injury or a history of alcohol abuse or dependence were allocated to the control group. Participants in the control group (n = 44) were approximately 72 years old (M = 71.5, SD = 6.1) with an average of 16.1 (SD = 2.1) years of education. Most (93.2%) participants in the group were right-handed. Thirty-nine (88.6%) participants were married with an additional 3 (6.8%) divorced. Thirty-one (70.5%) were retired. Most (84.1%) of the participants in the group were Caucasian.

Analysis of variance (ANOVA) was used to determine significant differences between groups on continuous demographic variables. Chi-squared test for independence was used to determine significant differences between groups in categorical demographic variables. There was no significant difference between groups in age ($p = 0.690$), handedness ($p = 0.183$), marital status ($p = 0.071$), years of education ($p = 0.653$), retirement status ($p = 0.166$) or race ($p = 0.327$; see Table 1).

Normality of Variables

Preliminary analyses were performed for all variables to ensure no violation of the assumptions of level of measurement, random sampling, independence of observation, normal distribution, and homogeneity of variance. Each of the dependent variables were continuous variables. Upon review of the dependent variables and their relationship with each other, it was determined that there was independence of observation for all measures. See Table 2 for a full description of variable normality.

Values of skewness and kurtosis were evaluated for normality. A score of .000 indicates no variability while scores of 1.00 and -1.00 indicate random scatter. Figure 1 shows relatively positively skewed scores on age. Figure 2 shows slightly negatively skewed scores on years of education with a large amount of variability. The assumption of normal distribution was violated for both age (k-s = 0.134, p = .001) and years of education (k-s = 0.168, p = .000).

Table 2.

Normality of variables

Variable	Minimum	Maximum	Skewness	Kurtosis	Kolmogorov-Smirnov	Sig.
Category Fluency (animals)	10	33	0.192	-0.259	0.085	0.200
Boston Naming Test	24	30	-1.220	1.146	0.252	0.000*
WMS-R Logical Memory I	2	20	-0.191	0.585	0.133	0.001*
WMS-R Logical Memory II	2	19	-0.186	0.264	0.093	0.071
RAVLT Trial 6	0	15	-0.203	-0.449	0.084	0.200
RAVLT Trial 7	0	14	0.307	-0.547	0.093	0.076
Trails A	11	92	1.639	5.559	0.111	0.013*
Trails B	39	264	2.258	7.962	0.155	0.000*
Geriatric Depression Scale	0	6	1.997	4.149	0.308	0.000*

WMS-R = Wechsler Memory Scale- Revised; RAVLT = Rey Auditory Verbal Learning Test; Trails = Trailmaking Test; *$p < 0.05$

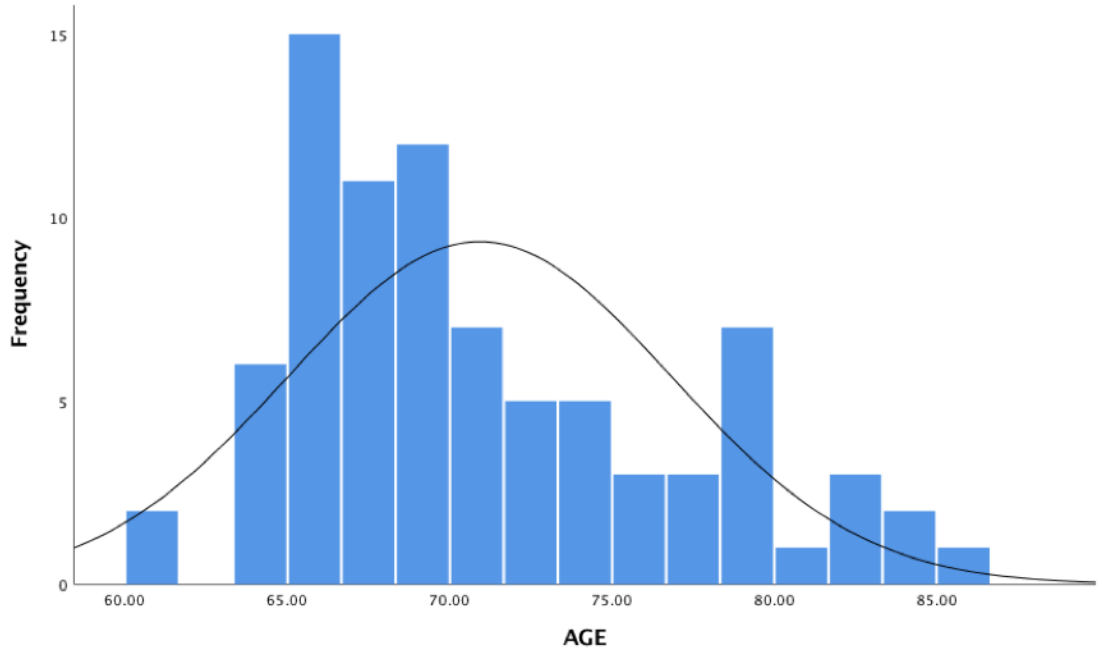

Figure 1. Histogram showing distribution of age for the total sample.

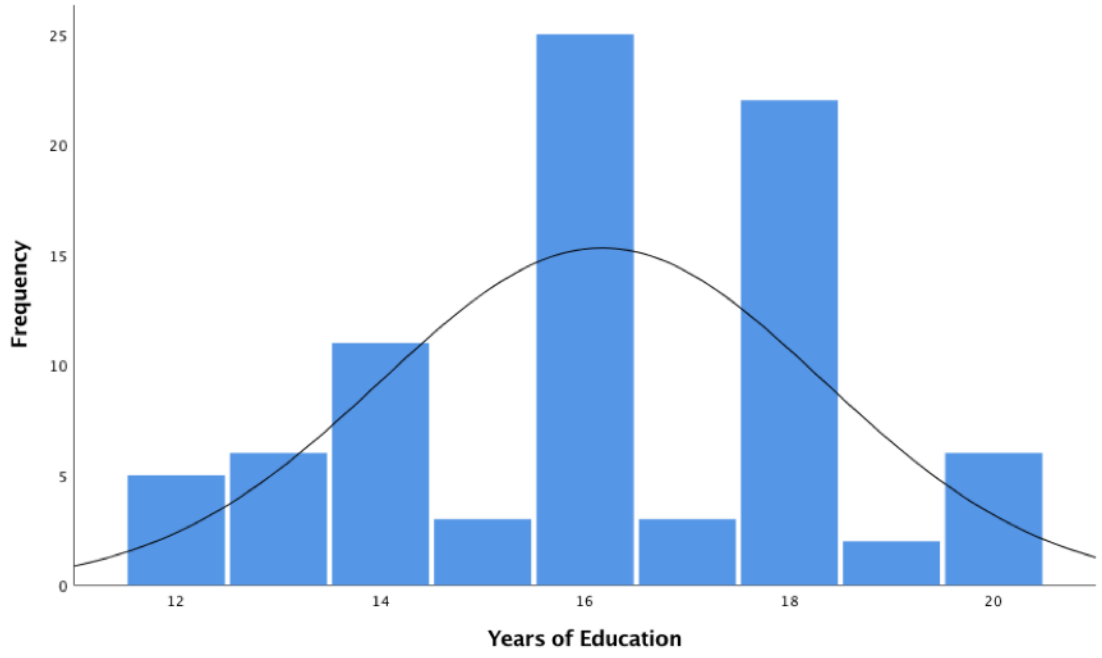

Figure 2. Histogram showing distribution of education for the total sample.

Category Fluency Test.

Normality was assessed for the continuous outcome variable of Category Fluency test total words produced (mean = 20.60, SD = 4.68). Using the 5% trimmed mean (20.56) compared to the original mean (20.60), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (0.19) indicated normal distribution due to it being far from 1.00. The value for kurtosis (-0.26) did not indicate abnormal distribution. The K-S value (K-S = 0.09; $p = 0.20$) was not significant, suggesting that the distribution was normal. A histogram confirmed the normal distribution of scores on the Category Fluency Test (see Figure 3). Furthermore, a boxplot of the scores indicated there were no outliers (see Figure 4). After running the one-way between-groups ANCOVA, homogeneity of variance was assessed using Levene's statistic ($p = 0.39$), and it was determined that the homogeneity of variance assumption was not violated because it was greater than the $p > .05$ cut-off value.

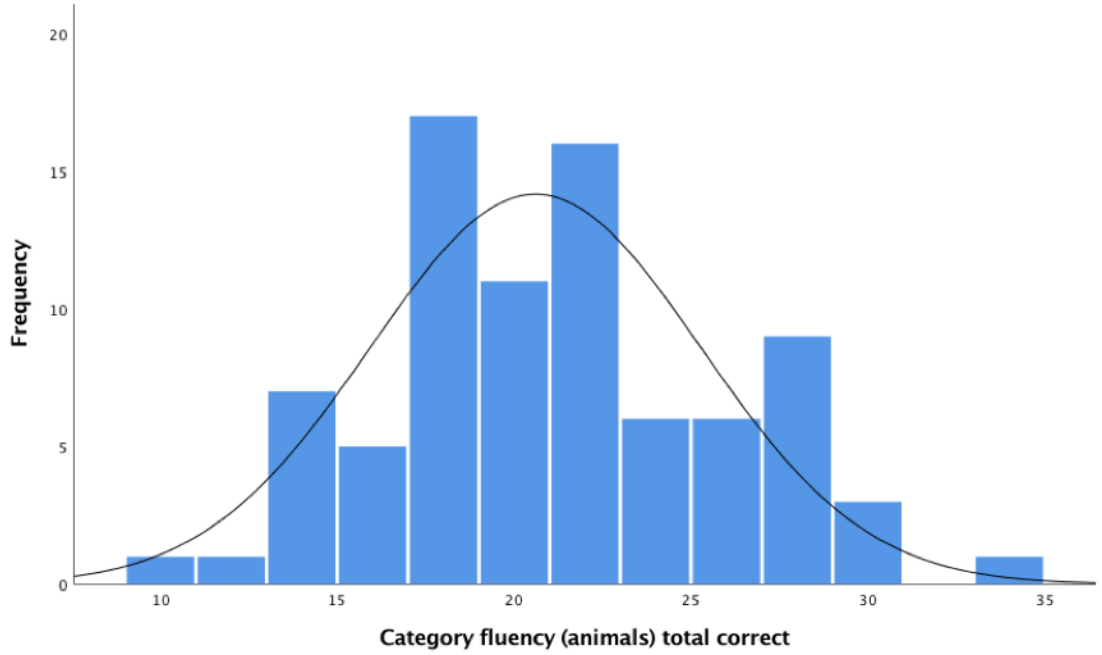

Figure 3. Histogram showing distribution of category fluency scores for the total sample.

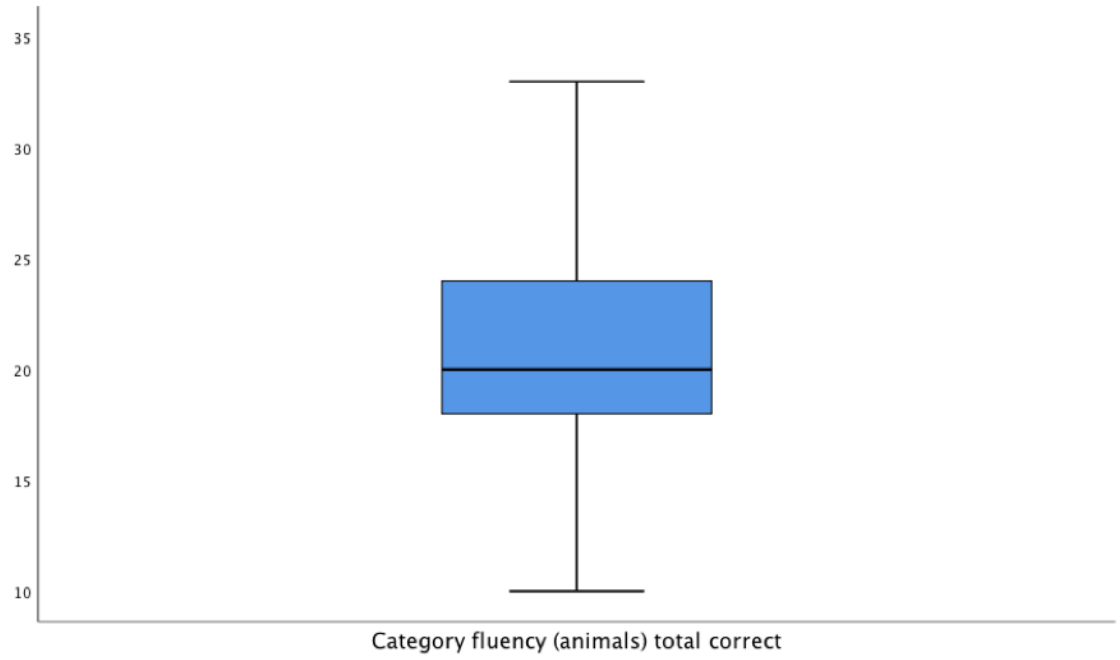

Figure 4. Boxplot showing outliers of category fluency scores.

Boston Naming Test.

Normality was assessed for the continuous outcome variable of Boston Naming Test total figures named (mean = 28.49, SD = 1.54). Using the 5% trimmed mean (28.64) compared to the original mean (28.49), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (-1.22) indicated abnormal distribution due to it being close to 1.00. The value for kurtosis (1.15) also indicated abnormal distribution. The K-S value (K-S = 0.25; $p = 0.00$) was significant, suggesting that the distribution was abnormal. A histogram confirmed the abnormal distribution of scores on the Boston Naming Test (see Figure 5). Furthermore, a boxplot of the scores indicated there were three possible outliers as indicated by three points lying outside of the boxplot whiskers (see Figure 6). Due to the assumption of normality not being met, a Kruskal-Wallace test was used as the non-parametric equivalent to the one-way between groups ANOVA.

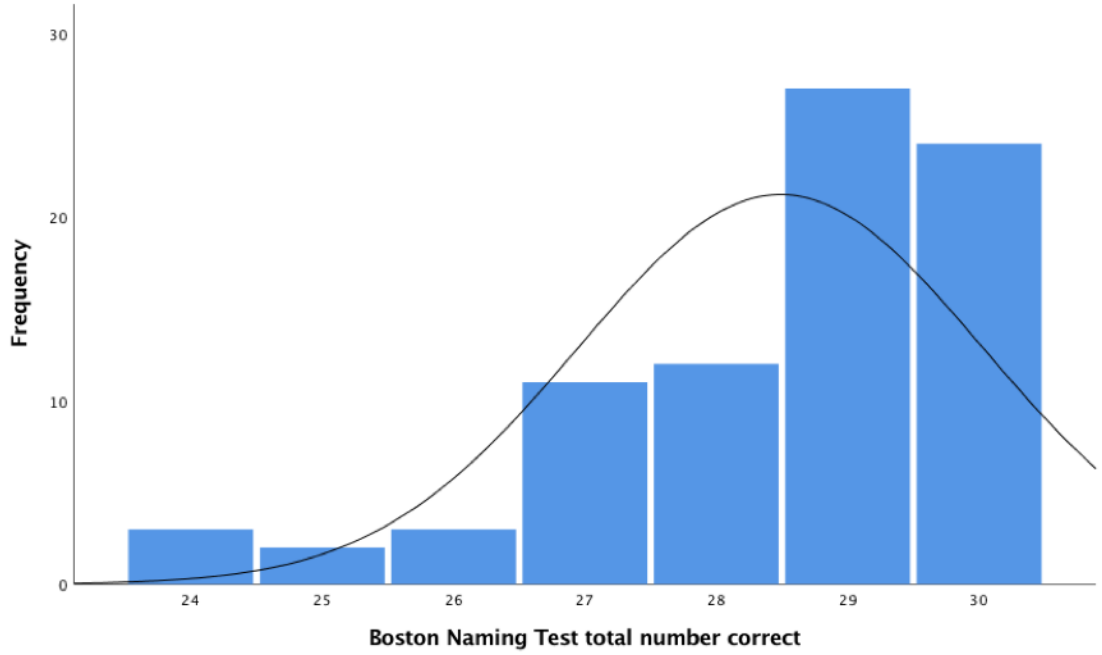

Figure 5. Histogram showing distribution of Boston Naming Test scores for the total sample.

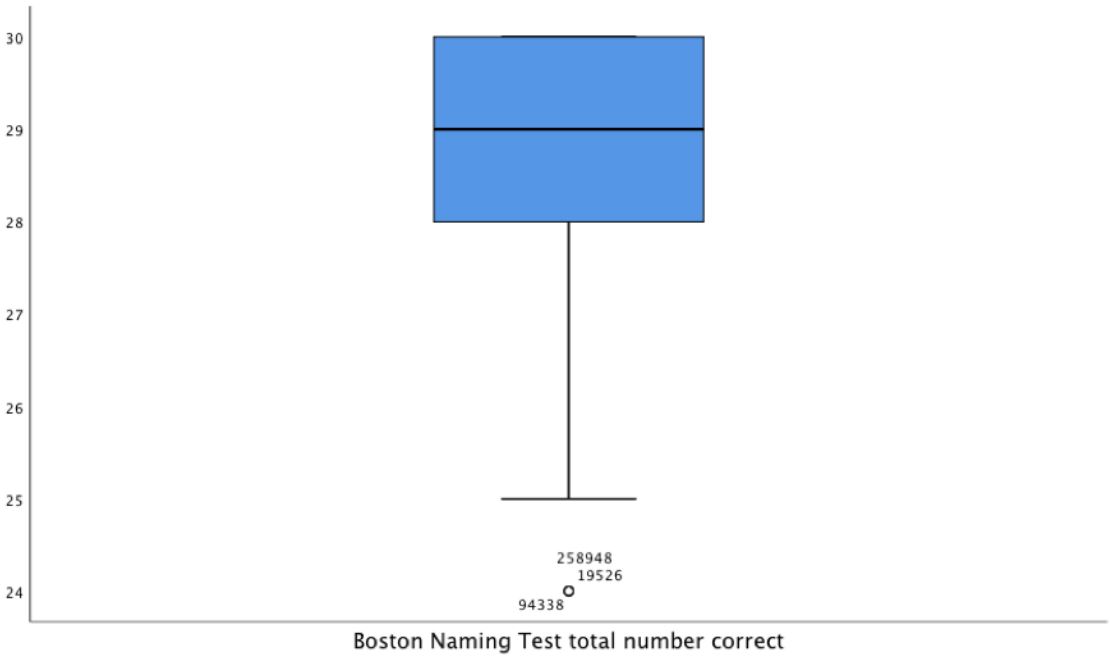

Figure 6. Boxplot showing outliers of Boston Naming Test scores

WMS-R Logical Memory I.

Normality was assessed for the continuous outcome variable of WMS-R Logical Memory I total score (mean = 12.05, SD = 3.25). Using the 5% trimmed mean (12.08) compared to the original mean (12.05), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (-0.19) indicated normal distribution due to it being far from 1.00. The value for kurtosis (0.585) indicated a slightly abnormal distribution. The K-S value (K-S = 0.13; $p = 0.01$) was significant, suggesting that the distribution was abnormal. A histogram confirmed the abnormal distribution of scores on the WMS-R Logical Memory I subtest (see Figure 7). Furthermore, a boxplot of the scores indicated there was one possible outlier as indicated by one point lying outside of the boxplot whiskers (see Figure 8). Due to the assumption of normality not being met, a Kruskal-Wallace test was used as the non-parametric equivalent to the one-way between groups ANOVA.

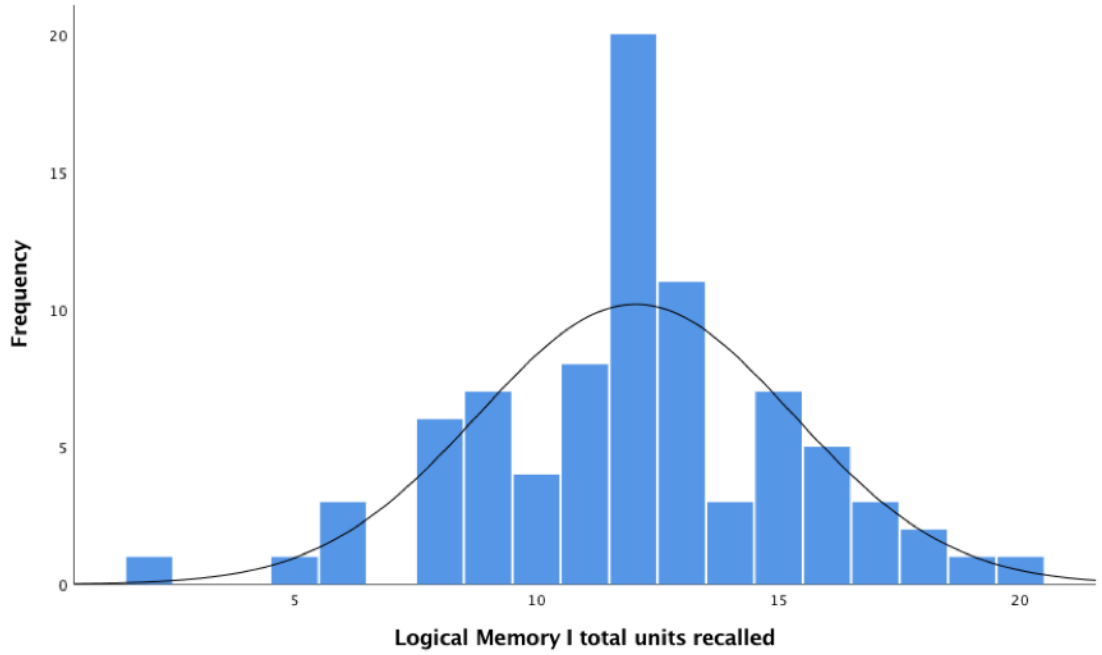

Figure 7. Histogram showing distribution of WMS-R Logical Memory I scores for the total sample

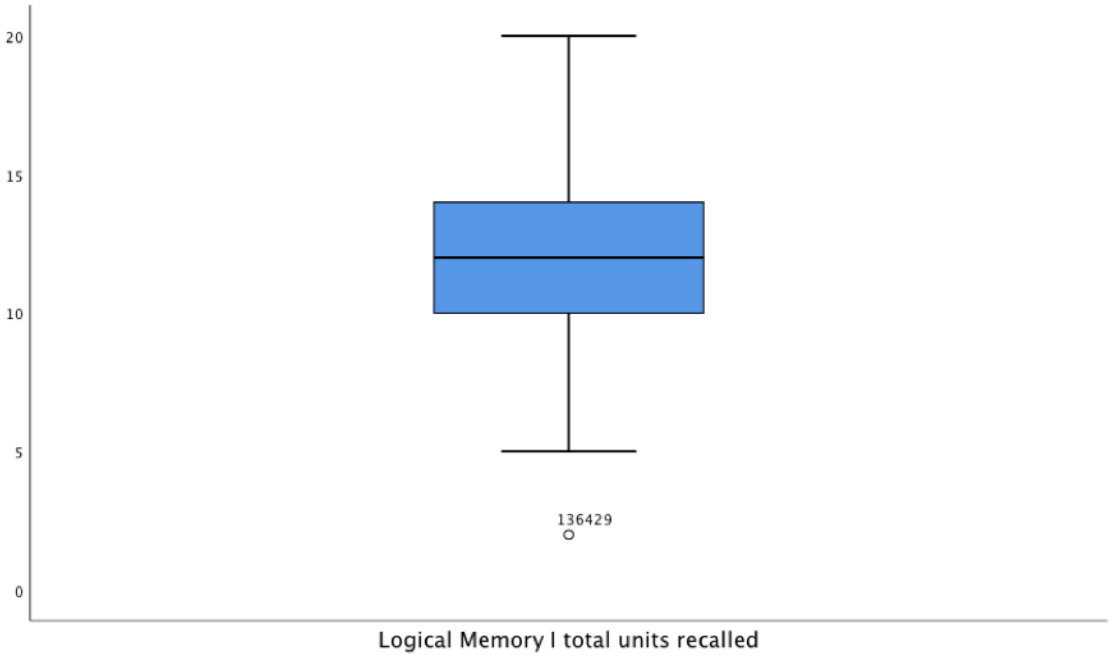

Figure 8. Boxplot showing outliers of WMS-R Logical Memory I scores

WMS-R Logical Memory II.

Normality was assessed for the continuous outcome variable of WMS-R Logical Memory II total score (mean = 10.69, SD = 3.66). Using the 5% trimmed mean (10.75) compared to the original mean (10.69), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (-0.19) indicated normal distribution due to it being far from 1.00. The value for kurtosis (0.09) did not indicate abnormal distribution. The K-S value (K-S = 0.09; $p = 0.07$) was not significant, suggesting that the distribution was normal. A histogram confirmed the normal distribution of scores on the WMS-R Logical Memory II subtest (see Figure 9). Furthermore, a boxplot of the scores indicated there were two possible outliers as indicated by two points lying outside of the boxplot whiskers (see Figure 10). After running the one-way between-groups ANCOVA, homogeneity of variance was assessed using Levene's statistic ($p = 0.08$), and it was determined that the homogeneity of variance assumption was not violated because it was greater than the $p > .05$ cut-off value.

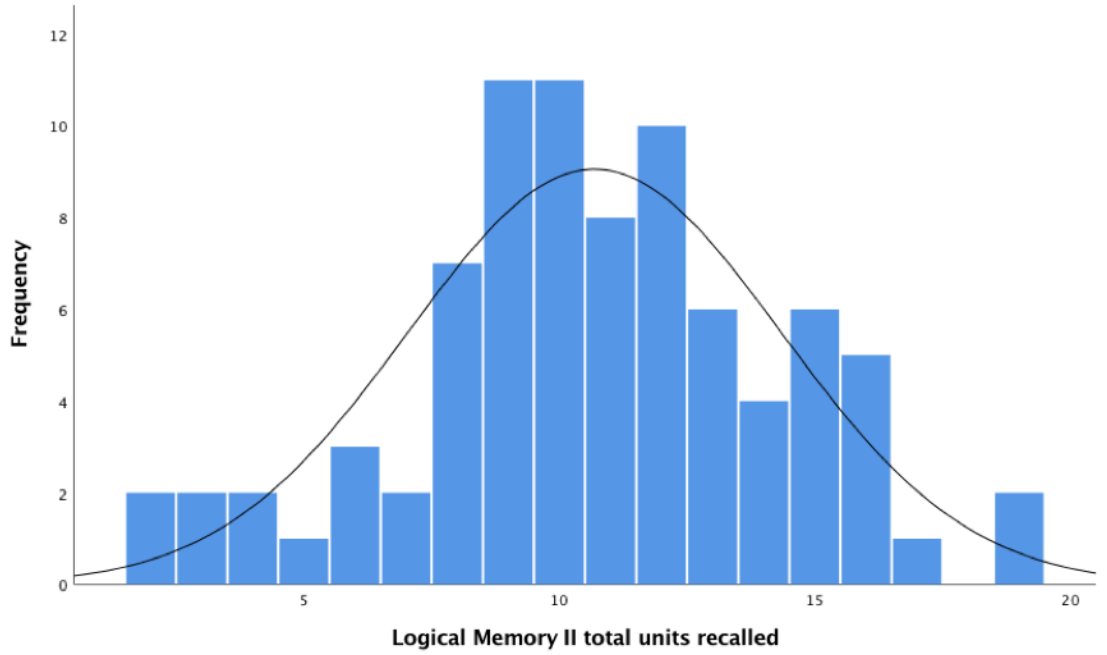

Figure 9. Histogram showing distribution of WMS-R Logical Memory II scores for the total sample.

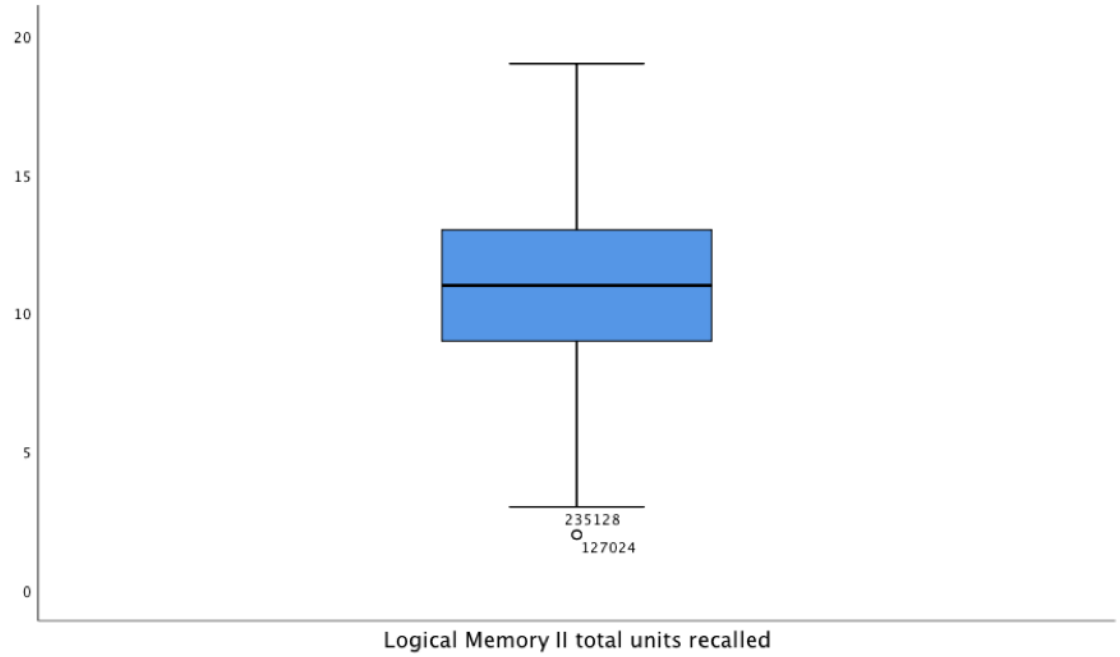

Figure 10. Boxplot showing outliers of WMS-R Logical Memory II scores.

Rey Auditory Verbal Learning Test trial 6.

Normality was assessed for the continuous outcome variable of the Rey Auditory Verbal Learning Test trial 6 total (mean = 7.46, SD = 3.51). Using the 5% trimmed mean (7.51) compared to the original mean (7.46), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (-0.20) indicated normal distribution due to it being far from 1.00. The value for kurtosis (-0.45) did not indicate abnormal distribution. The K-S value (K-S = 0.08; $p = 0.20$) was not significant, suggesting that the distribution was normal. A histogram confirmed the normal distribution of scores on the RAVLT trial 6 (see Figure 11). Furthermore, a boxplot of the scores indicated there were no outliers (see Figure 12). After running the one-way between-groups ANCOVA, homogeneity of variance was assessed using Levene's statistic ($p = 0.45$), and it was determined that the homogeneity of variance assumption was not violated because it was greater than the $p > .05$ cut-off value.

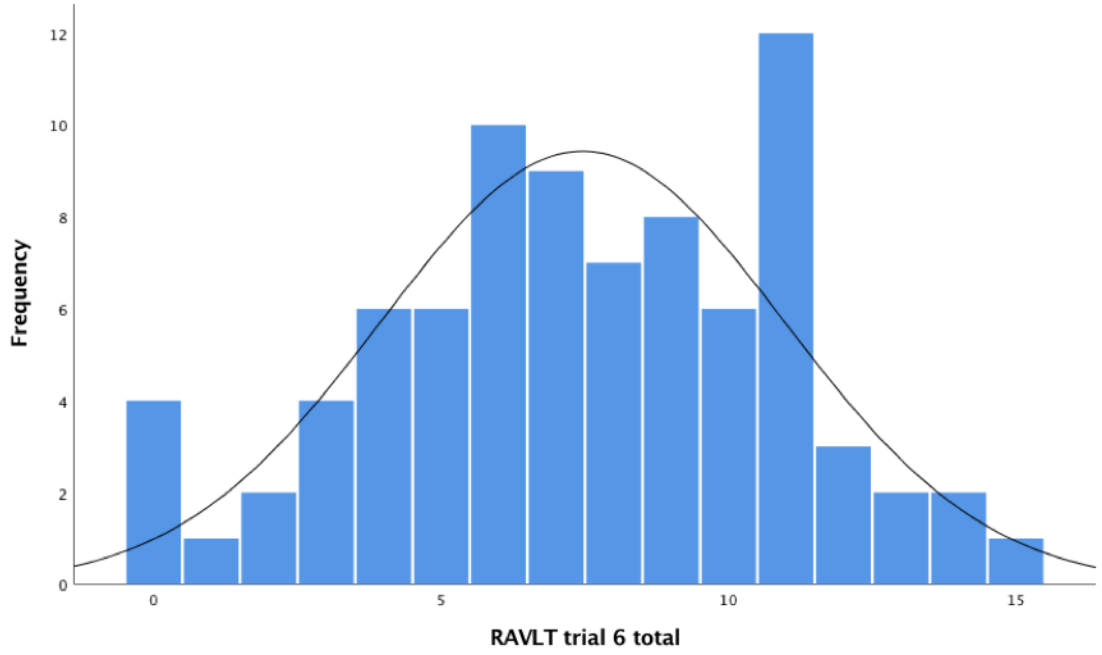

Figure 11. Histogram showing distribution of RAVLT trial 6 scores for the total sample.

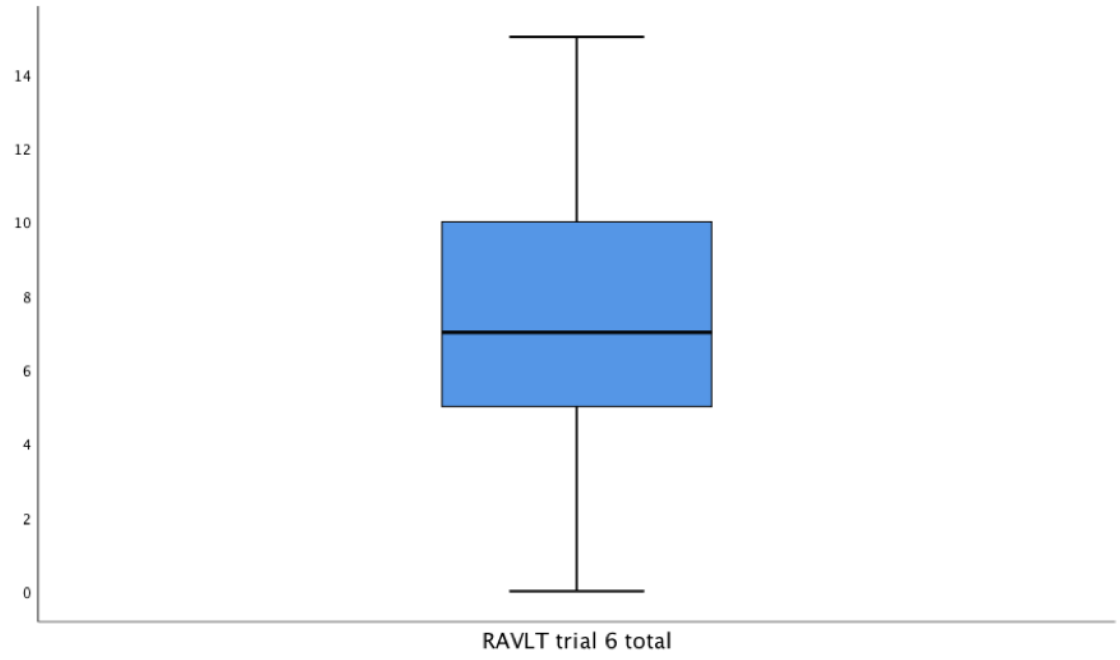

Figure 12. Boxplot showing outliers of RAVLT trial 6 scores.

Rey Auditory Verbal Learning Test trial 7.

Normality was assessed for the continuous outcome variable of Rey Auditory Verbal Learning Test trial 7 (mean = 5.76, SD = 3.73). Using the 5% trimmed mean (5.65) compared to the original mean (5.76), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (0.31) indicated normal distribution due to it being far from 1.00. The value for kurtosis (-0.55) did not indicate abnormal distribution. The K-S value (K-S = 0.09; $p = 0.08$) was not significant, suggesting that the distribution was normal. A histogram confirmed the normal distribution of scores on the RAVLT trial 7 (see Figure 13). Furthermore, a boxplot of the scores indicated there were no outliers (see Figure 14). After running the one-way between-groups ANCOVA, homogeneity of variance was assessed using Levene's statistic ($p = 0.73$) and it was determined that the homogeneity of variance assumption was not violated because it was greater than the $p > .05$ cut-off value.

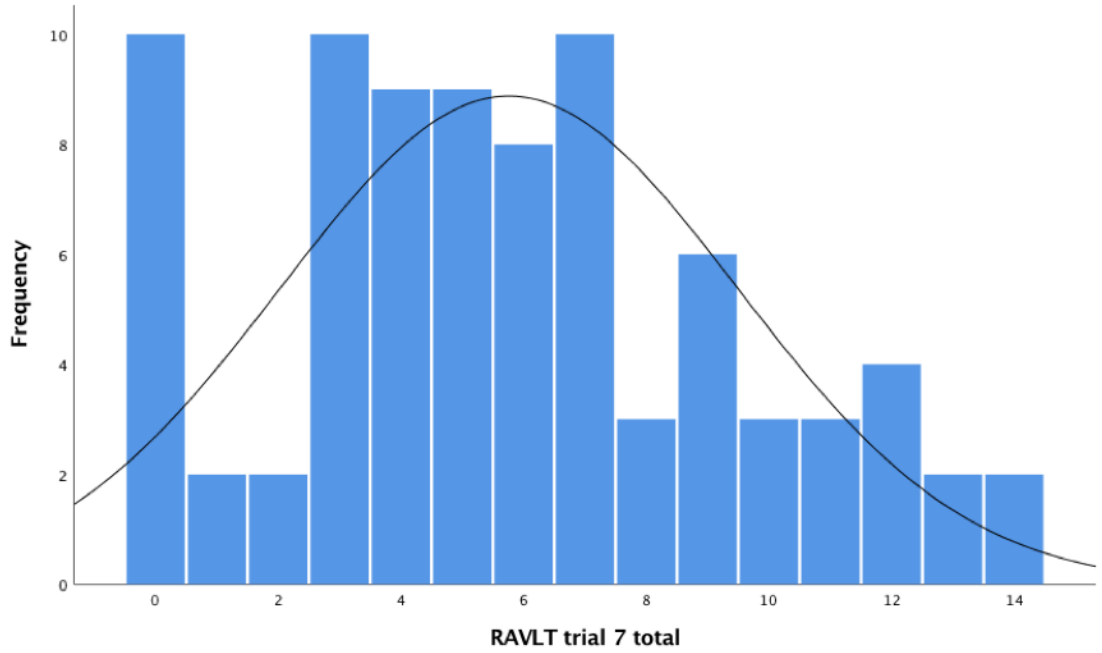

Figure 13. Histogram showing distribution of RAVLT trial 7 scores for the total sample.

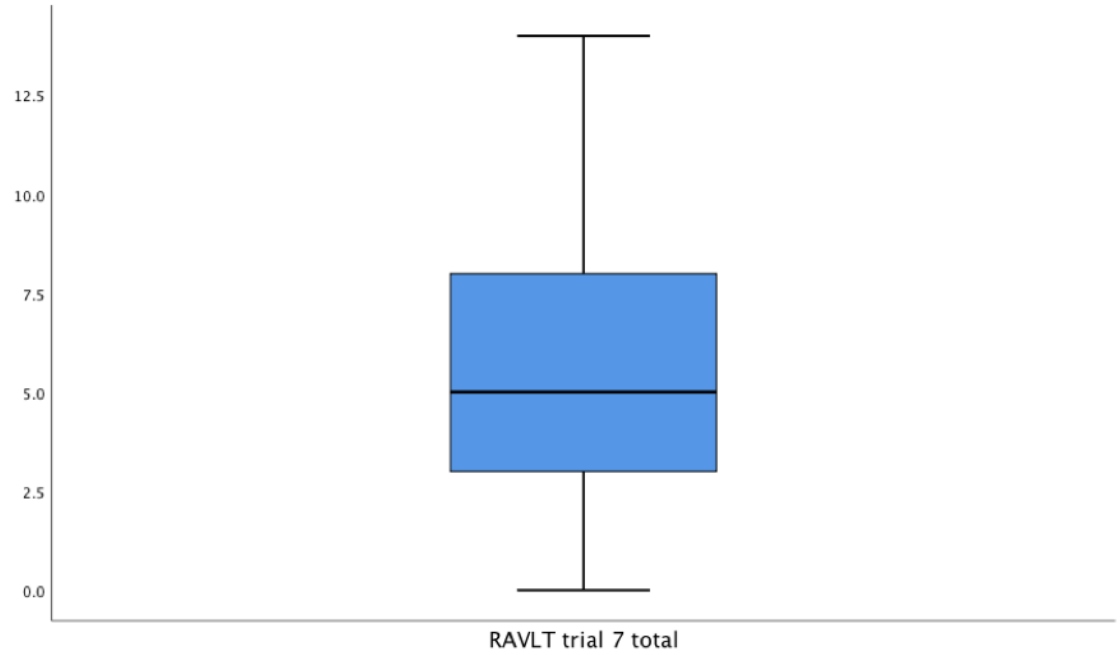

Figure 14. Boxplot showing outliers of RAVLT trial 7 scores

Trailmaking Test A.

Normality was assessed for the continuous outcome variable of Trailmaking Test A time to complete (mean = 35.08, SD = 11.92). Using the 5% trimmed mean (34.17) compared to the original mean (35.08), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (-1.64) indicated abnormal distribution due to it being close to 1.00. The value for kurtosis (5.56) also indicated abnormal distribution. The K-S value (K-S = 0.11; $p = 0.01$) was significant, suggesting that the distribution was abnormal. A histogram confirmed the abnormal distribution of scores on the Trailmaking Test A (see Figure 15). Furthermore, a boxplot of the scores indicated there were four possible outliers as indicated by four points lying outside of the boxplot whiskers (see Figure 16). Due to the assumption of normality not being met, a Kruskal-Wallace test was used as the non-parametric equivalent to the one-way between groups ANOVA.

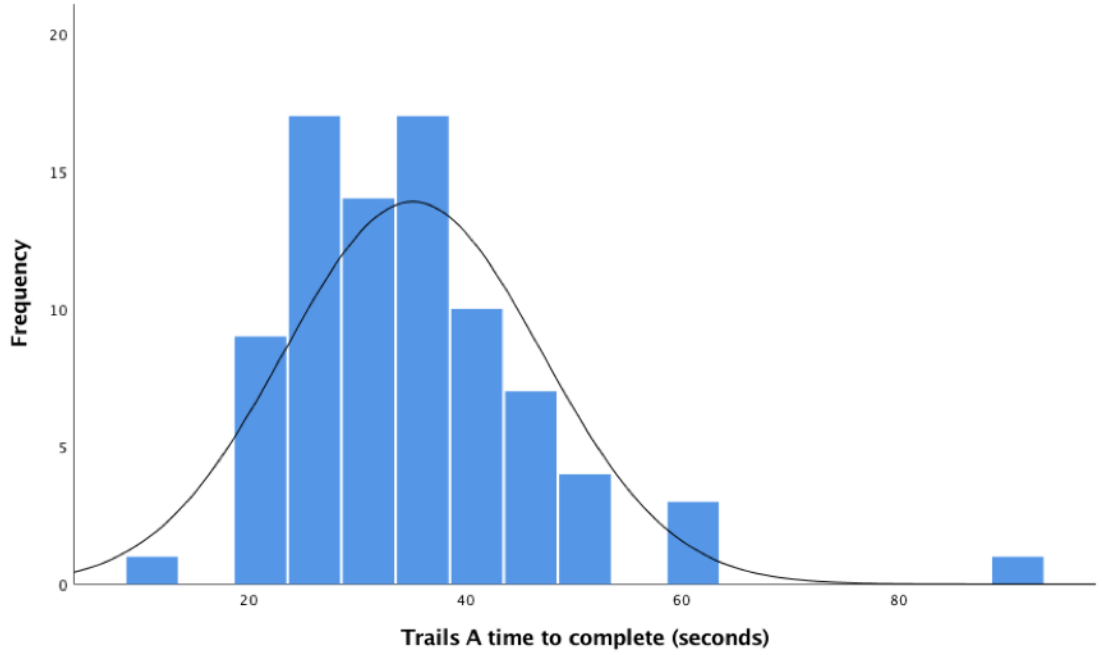

Figure 15. Histogram showing distribution of Trails A completion time for the total sample.

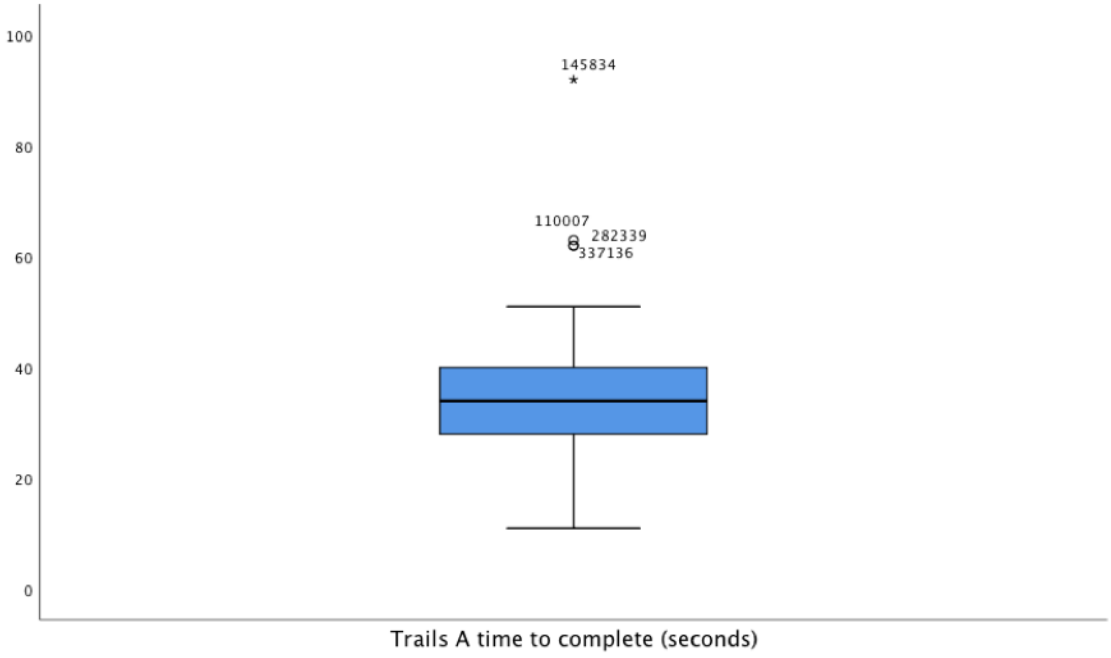

Figure 16. Boxplot showing outliers of trails A completion time

Trailmaking Test B.

Normality was assessed for the continuous outcome variable of Trailmaking Test B time to complete (mean = 87.53, SD = 35.00). Using the 5% trimmed mean (83.93) compared to the original mean (87.53), it was determined that there were possibly some extreme values influencing the mean of the data. The value for skew (2.26) indicated abnormal distribution due to it being close to 1.00. The value for kurtosis (7.96) also indicated abnormal distribution. The K-S value (K-S = 0.16; p = 0.00) was significant, suggesting that the distribution was abnormal. A histogram confirmed the abnormal distribution of scores on the Trailmaking Test B (see Figure 17). Furthermore, a boxplot of the scores indicated there were five possible outliers as indicated by five points lying outside of the boxplot whiskers (see Figure 18). Due to the assumption of normality not being met, a Kruskal-Wallace test was used as the non-parametric equivalent to the one-way between groups ANOVA.

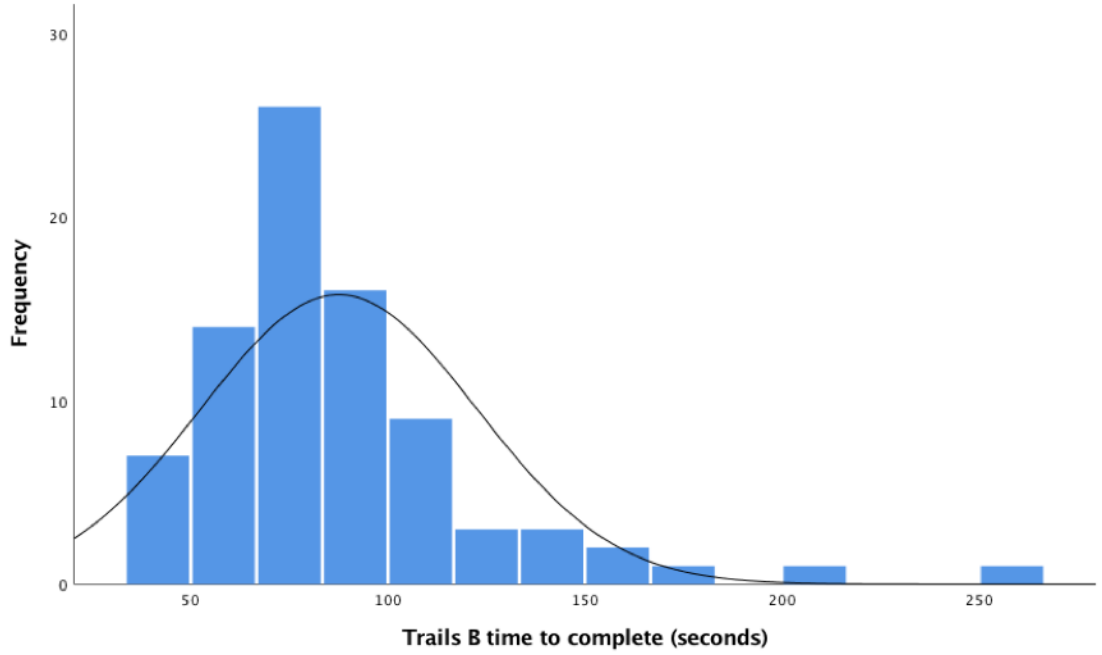

Figure 17. Histogram showing distribution of Trails B completion time for the total sample.

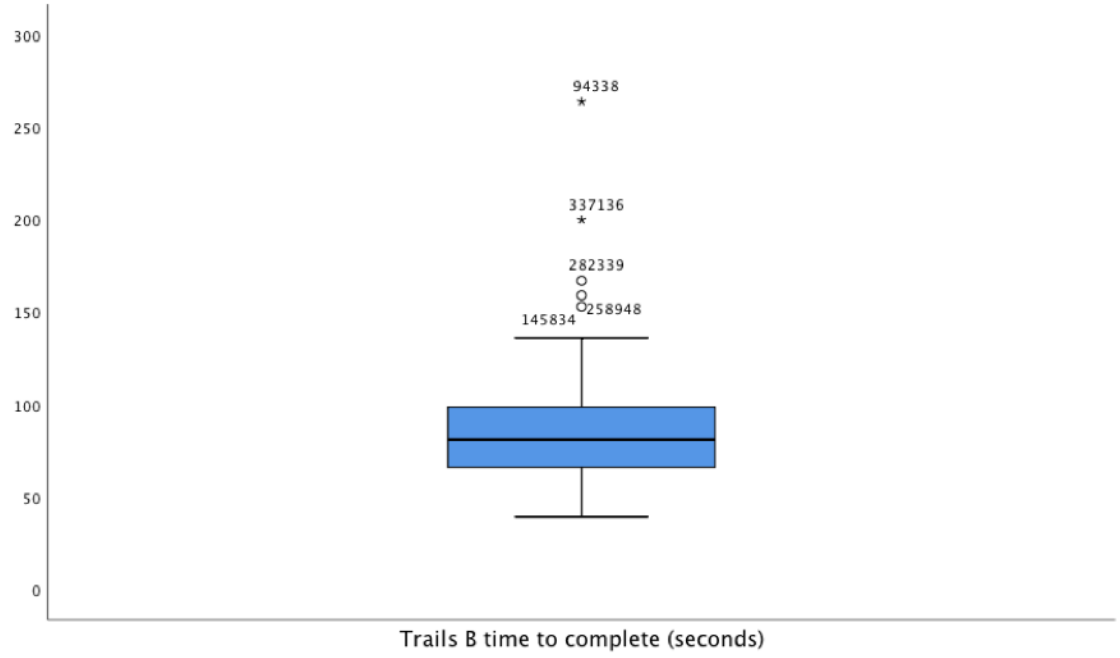

Figure 18. Boxplot showing outliers of Trails B completion time.

Geriatric Depression Scale.

Normality was assessed for the continuous outcome variable of Geriatric Depression Scale total (mean = 0.84, SD = 1.30). Using the 5% trimmed mean (0.66) compared to the original mean (0.84), it was determined that there were not any extreme values influencing the mean of the data. The value for skew (2.00) indicated abnormal distribution due to it being close to 1.00. The value for kurtosis (4.15) also indicated abnormal distribution. The K-S value (K-S = 0.31; $p = 0.00$) was significant, suggesting that the distribution was abnormal. A histogram confirmed the abnormal distribution of scores on the Geriatric Depression Scale (see Figure 19). Furthermore, a boxplot of the scores indicated there were seven possible outliers as indicated by seven points lying outside of the boxplot whiskers (see Figure 20). Due to the assumption of normality not being met, a Kruskal-Wallace test was used as the non-parametric equivalent to the one-way between groups ANOVA.

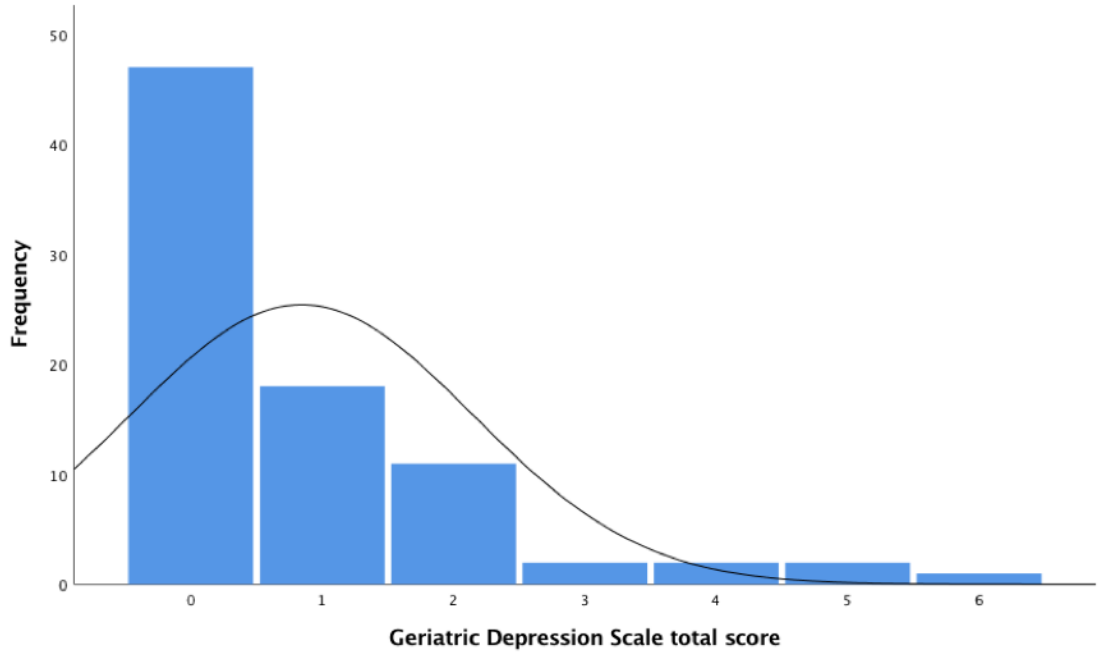

Figure 19. Histogram showing distribution of Geriatric Depression Scale scores for the total sample

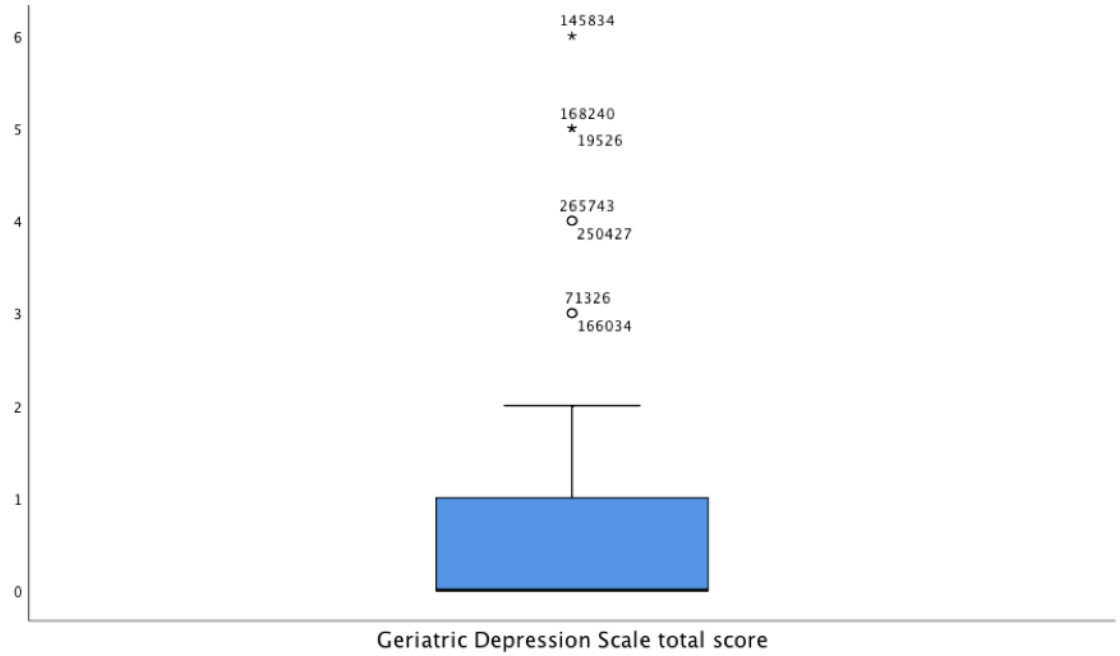

Figure 20. Boxplot showing outliers of Geriatric Depression Scale scores

Neuropsychological Variable Analyses

All neuropsychological variables were analyzed to determine statistically significant differences between groups. Table 3 outlines the differences between groups on normally distributed neuropsychological variables. Table 4 outlines differences between groups on neuropsychological variables while accounting for the effects of age, education level, and presence of the ApoE E4 allele variant. Each neuropsychological measure is detailed below. Table 5 outlines differences between groups on neuropsychological variables which were not normally distributed. There were no differences between groups on neuropsychological measures.

Table 3.

One-way ANOVA comparing neuropsychological performance between groups.

Variable	n	Mean	Median	F	Sig.
Category Fluency				0.103	0.903
TBI-Alcohol	10	20.20	20.50		
TBI-No Alcohol	29	20.90	21.00		
Control	44	20.50	20.00		
WMS-R Logical Memory II				0.316	0.730
TBI-Alcohol	10	10.20	10.50		
TBI-No Alcohol	29	11.10	10.00		
Control	44	10.52	11.00		
RAVLT trial 6				0.029	0.971
TBI-Alcohol	10	7.40	6.50		
TBI-No Alcohol	29	7.34	7.00		
Control	44	7.55	8.00		
RAVLT trial 7				0.251	0.779
TBI-Alcohol	10	6.30	5.50		
TBI-No Alcohol	29	5.97	5.00		
Control	44	5.50	6.00		

WMS-R = Wechsler Memory Scale- Revised; RAVLT = Rey Auditory Verbal Learning Test; all *$p > 0.05$

Table 4.

Univariate analysis of variance controlling for age, education level, and ApoE E4.

Variable	n	Adjusted Mean	F	Sig.	Partial eta squared
Category Fluency			0.051	0.950	0.001
TBI-Alcohol	10	20.21			
TBI-No Alcohol	29	20.77			
Control	44	20.58			
WMS-R Logical Memory II			0.165	0.848	0.004
TBI-Alcohol	10	10.28			
TBI-No Alcohol	29	10.97			
Control	44	10.59			
RAVLT trial 6			0.166	0.847	0.004
TBI-Alcohol	10	7.38			
TBI-No Alcohol	29	7.19			
Control	44	7.66			
RAVLT trial 7			0.118	0.889	0.003
TBI-Alcohol	10	6.19			
TBI-No Alcohol	29	5.85			
Control	44	5.60			

WMS-R = Wechsler Memory Scale- Revised; RAVLT = Rey Auditory Verbal Learning Test; all *p >0.05

Table 5.

Kruskal-Wallis test for neuropsychological variables with non-normal distribution.

Variable	n	Mean rank	Median	Kruskal-Wallis H	Sig.
Boston Naming Test	83			4.574	0.102
TBI-Alcohol	10	32.10	28.00		
TBI-No Alcohol	29	38.03	29.00		
Control	44	46.86	29.00		
WMS-R Logical Memory I	83			0.381	0.827
TBI-Alcohol	10	43.70	12.50		
TBI-No Alcohol	29	39.81	12.00		
Control	44	43.06	12.00		
Trails A	83			1.843	0.398
TBI-Alcohol	10	39.55	31.00		
TBI-No Alcohol	29	37.78	30.00		
Control	44	45.34	35.00		
Trails B	83			0.527	0.768
TBI-Alcohol	10	43.95	79.50		
TBI-No Alcohol	29	39.40	79.00		
Control	44	43.27	83.00		
Geriatric Depression Scale	83			3.958	0.138
TBI-Alcohol	10	38.55	0.00		
TBI-No Alcohol	29	48.45	1.00		
Control	44	38.53	0.00		

WMS-R = Wechsler Memory Scale- Revised; Trails = Trailmaking Test; *$p < 0.05$

Category Fluency Test.

A one-way ANOVA was conducted to determine the effects of TBI and alcohol use on semantic fluency as measured by the category fluency test animal naming. There was no significant difference between groups in animal naming scores F (2, n = 83) = 0.103, p = 0.903 (see Table 3). To control for the possible effects of age, level of education, and ApoE E4 allele variant presence, a one-way ANCOVA was also conducted. There remained no difference between the groups in animal naming scores F (2, n = 75) = 0.177, p = 0.838 (see Table 4).

Boston Naming Test.

A Kruskal-Wallis Test determined there was no significant differences on the Boston Naming Test across three different groups (TBI-Alcohol, n = 10; TBI-No Alcohol, n = 29; Control, n = 44), H (2, n = 83 = 4.574, p = 0.102 with a mean rank naming score of 32.10 for the TBI-Alcohol group, 38.03 for the TBI-No Alcohol group, and 46.86 for the Control group. The median for the TBI-Alcohol group was lower (Md = 28) than the TBI-No Alcohol group (Md = 29) and the Control group (Md = 29; see Table 5).

WMS-R Logical Memory I.

A Kruskal-Wallis Test determined there was no significant differences on the WMS-R Logical Memory I subtest across three groups (TBI-Alcohol, n = 10; TBI-No Alcohol, n = 29; Control, n = 44), H (2, n = 83) = 0.381, p = 0.827 with a mean rank immediate story recall score of 43.70 for the TBI-Alcohol group, 39.81 for the TBI-No Alcohol group, and 43.06 for the Control group. All three groups recorded a median score of zero (see Table 5).

WMS-R Logical Memory II.

A one-way ANOVA was conducted to determine the effects of TBI and alcohol use on delayed story memory as measured by the WMS-R Logical Memory II subtest. There was no significant difference between groups in delayed story memory scores F (2, n = 83) = 0.316, p = 0.730 (see Table 3). To control for the possible effects of age, level of education, and ApoE E4 allele variant presence, a one-way ANCOVA was also conducted. There remained no difference between the groups in delayed story memory scores F (2, n = 83) = 0.165, p = 0.848 (see Table 4).

Rey Auditory Verbal Learning Test trial 6.

A one-way ANOVA was conducted to determine the effects of TBI and alcohol use on immediate verbal recall as measured by the Rey Auditory Verbal Learning Test trial 6. There was no significant difference between groups in immediate verbal memory scores F (2, n = 83) = 0.029, p = 0.971(see Table 3). To control for the possible effects of age, level of education, and ApoE E4 allele variant presence, a one-way ANCOVA was also conducted. There remained no difference between the groups in immediate verbal memory scores F (2, n = 83) = 0.166, p = 0.847 (see Table 4).

Rey Auditory Verbal Learning Test trial 7.

A one-way ANOVA was conducted to determine the effects of TBI and alcohol use on delayed verbal recall as measured by the Rey Auditory Verbal Learning Test trial 7. There was no significant difference between groups in delayed verbal memory scores F (2, n = 83) = 0.251, p = 0.779 (see Table 3). To control for the possible effects of age, level of education, and ApoE E4 allele variant presence, a one-way ANCOVA was also conducted. There remained no difference between the groups in delayed verbal memory scores F (2, n = 83) = 0.118, p = 0.889 (see Table 4).

Trailmaking Test A.

A Kruskal-Wallis Test determined there was no significant differences on Trailmaking Test A across three groups (TBI-Alcohol, n = 10; TBI-No Alcohol, n = 29; Control, n = 44), H (2, n = 83) = 1.843, p = 0.398 with a mean rank completion time of 39.55 for the TBI-Alcohol group, 37.78 for the TBI-No Alcohol group, and 45.34 for the control group. The median completion time was highest for the Control group (Md = 35.00 seconds) followed by the TBI-

Alcohol group (Md = 31.00 seconds) and TBI-No Alcohol group (Md = 30.00 seconds; see Table 5).

Trailmaking Test B.

A Kruskal-Wallis Test determined there was no significant differences on Trails B across three groups (TBI-Alcohol, n = 10; TBI-No Alcohol, n = 29; Control, n = 44), H (2, n = 83) = 0.527, $p = 0.768$ with a mean rank completion time of 43.95 for the TBI-Alcohol group, 39.40 for the TBI-No Alcohol group, and 43.27 for the Control group. The median completion time was highest for the Control group (Md = 83.00 seconds) followed by the TBI-Alcohol group (Md = 79.50 seconds) and the TBI-No Alcohol group (Md = 75.00 seconds; see Table 5).

Geriatric Depression Scale.

A Kruskal-Wallis Test determined there was no significant differences on the Geriatric Depression Scale across three groups (TBI-Alcohol, n = 10; TBI-No Alcohol, n = 29; Control, n = 44), H (2, n = 83) = 3.958, $p = 0.138$ with a mean rank total depression score of 38.55 for the TBI-Alcohol group, 48.45 for the TBI-No Alcohol group, and 38.53 for the Control group. The median depression score was highest for the TBI-No Alcohol group (Md = 1.00) followed by the TBI-Alcohol group (Md = 0.00) and the Control group (Md = 0.00; see Table 5).

CHAPTER V: DISCUSSION

The present study sought to understand the impact that a history of alcohol use has on the neuropsychological functioning of older adults who have experienced a traumatic brain injury. Much of the existing literature sheds light on disorders and disabilities more likely to be found in older adults, such as mild cognitive impairment/Alzheimer's disease. Surprisingly, far less research is conducted on acquired brain injury in older adults even though they are far more likely to obtain a head injury than their younger adult counterparts. It is commonly agreed upon that a history or moderate-severe traumatic brain injury or alcohol abuse and dependence negatively impact neuropsychological functioning with increasing age. The primary goal for the current study was to determine the interaction effects of lifetime traumatic brain injury and alcohol abuse and compare these groups with healthy controls to determine if the relationship is clinically significant.

The results of the current study were extremely surprising and contrary to much of the literature in the areas of cognitive decline, traumatic brain injury, and alcohol abuse. A history of alcohol abuse or dependence did not exacerbate neuropsychological functioning decline when compared to groups that did not have a history of alcohol abuse. These findings are contrary to the work of many researchers (Bombardier & Thurber, 1998; Kelly, Johnson, Knoller, & Drubach, 1997; Tate, Freed, Bombardier, Harter, & Brinkman, 1999; Wilde et al., 2004) who found alcohol presence to negatively impact a variety of neuropsychological domains following a traumatic brain injury. Findings are consistent, however, with other research (Bendszus et al., 2001; Fein, Torres, Price, & Di Sclafani, 2006; Pitel et al., 2009) who suggest cognitive recovery is possible with prolonged abstinence from alcohol, albeit without the confounding factor of a traumatic brain injury.

Overall, the results from the current study provide no evidence that a history of alcohol abuse or dependence negatively impacts older adults with a history of traumatic brain injury any more than the traumatic brain injury alone. The findings might imply that alcohol use does not negatively affect cognition or that the short-term effects of alcohol abuse are primarily mediated by prolonged abstinence. Readers are cautioned that there is an extensive literature base for the structural and functional repercussions of prolonged alcohol use alone absent of a traumatic brain injury (Trivedi et al., 2013; Brown, Tapert, Grahholm, & Delis, 2000; Scheurich, 2005).

The hypothesis that the group with a history of alcohol abuse or dependence will produce fewer words than the group with no history of alcohol abuse or dependence in one minute was not supported. The results of the current study are consistent with the earlier findings of Fein, Torres, Price, & Di Sclafani (2006) who found no difference between alcohol abusing and abstinent males on COWAT. Similar findings were replicated on a longitudinal study suggesting heavier alcohol use projected a significant decline in verbal fluency, but not semantic fluency (Topiwala et al., 2017). The findings imply that alcohol is not a likely contributor to verbal fluency deficits in individuals with a history of traumatic brain injury if they have not met diagnostic criteria for alcohol abuse or dependence in five years, which was an exclusion criterion of the current study. The hypothesis that the group with a history of alcohol abuse or dependence will correctly name significantly fewer pictures than those without a history of alcohol abuse or dependence was not supported. Consistent with the current literature (Topiwala et al., 2017), confrontation naming appears to be stable in individuals with a period of abstinence.

The hypothesis that the group with a history of alcohol abuse or dependence will recall fewer details than the group with no history of alcohol abuse or dependence on Logical Memory

I total score was not supported. Additionally, the hypothesis that there will be no significant difference between the groups on the total score of logical memory II was supported. The literature on verbal memory decline following alcohol abuse is variable. Some evidence is in support of significant verbal memory decline (Eckardt, Stapleton, Rawlings, Davis, & Grodin, 1995) whereas other literature describes negligible effects on verbal memory (Fein, Torres, Price, & Di Sclafani, 2006). The findings from the current study support the notions that immediate and delayed verbal memory functioning can recover following a period of abstinence.

The hypothesis that there will be no difference between the groups on the number of words produced on RAVLT trial 6 was supported. The hypothesis that there will be no difference between the groups on the number of words produced on RAVLT trial 7 was also supported. These findings are largely consistent with the findings of prior research (Fein, Torres, Price, & Di Sclafani, 2006) that short term verbal memory is not significantly worse in individuals with a history of alcohol abuse. Research suggests that an abstinence period of at least five weeks can mediate the effects of chronic alcohol use on verbal memory recovery (Bendszus et al., 2001; Pitel et al., 2009).

The hypothesis that there will be no difference between the groups on the speed in which it takes them to complete Trailmaking Test A was supported. The finding that speeded processing was not impacted by a lifetime history of alcohol abuse or dependence is consistent with prior research that abstinence can resolve processing speed deficits (Bendszus et al., 2001; Fein, Torres, Price, & Di Sclafani, 2006; Pitel et al., 2009). It is possible that the use of compensatory strategies learned following a traumatic brain injury counteracts the decline in processing speed due to the healthy aging process.

The hypothesis that the group with a history of alcohol abuse or dependence will complete Trailmaking Test B significantly slower than the group without a history of alcohol abuse or dependence was not supported. The results are again consistent with the field of research indicating abstinence plays a role in the recovery of functioning (Bendszus et al., 2001; Fein, Torres, Price, & Di Sclafani, 2006; Pitel et al., 2009).

The hypothesis that the group with a history of alcohol abuse or dependence will show significantly more depression than the group without a history of alcohol abuse or dependence was not supported. These findings differ from previous research (Zeigler et al., 2005) that found depression to be common in alcohol abusers due to loss of neurons in the locus coeruleus.

There are many possible explanations for the interesting results of the current study. The most obvious explanation is that cognitive recovery following prolonged drinking allowed individuals in that group to perform similarly to their peers. It is also likely that the small sample size and uneven distribution amongst the groups did not provide the most accurate representation of the larger population of alcohol abusers and individuals with traumatic brain injury. Additionally, self-report was the primary source of information when allocating the individuals to their respective groups. Although structured interviews provide an excellent opportunity for standardization, the participants are free to respond as they interpret the question, without the basis of a true diagnosis.

The clinical application of the current findings provides insight into functional recovery following traumatic brain injury and alcohol abuse as well as expected cognitive abilities of older adults. The relationship between alcohol and traumatic brain injury has primarily been studied within the context of the day-of-injury. The current study sheds light on the implications of

lifetime alcohol abuse and traumatic brain injury and how functioning is impacted in older adults.

The current study some limitations that might be addressed in future research. The glaring limitation to the current study is the uneven distribution of participants across the three groups. Even though the sample size for the experimental groups was small, the effect sizes presented shows no indication that the differences between groups would reach statistical significance with a larger sample size. It would be beneficial to perform a similar research study using the methodology described in the current study with an equal group distribution. In terms of the sample selected, all participants were located in one specific region of the country. Expanding the study to other regions with diverse demographic landscapes might provide a more heterogeneous sample, making results more generalizable to the public. There were many variables related to drinking alcohol that were not included in the current study. Understanding the length of abstinence and duration of alcohol use would provide a deeper level of understanding of the current results. Additionally, the current study did not differentiate between alcohol abuse and alcohol dependence. This distinction might further describe the changes in cognition or lack thereof. The current study also had strengths that should be considered during future studies. The sample was largely homogenous in terms of demographic variables which minimized the opportunity for confounding factors influencing outcomes. The current study also provided a large variety of neuropsychological variables examining many different domains of functioning known to be affected by alcohol and TBI. Future research should provide a longitudinal perspective to further understand the trajectory of neuropsychological functioning from injury to older adulthood in individuals who use alcohol excessively.

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